The neuromodulatory properties of gonadal steroid hormones with regard to individual differences in cognition and brain organisation.

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Declaration

I confirm that no part of the material offered has previously been submitted by me for a degree in this or in any other University. If material has been generated through joint work, my independent contribution has been clearly indicated. In all other cases material from the work of others has been acknowledged and quotations and paraphrases suitably indicated.

Statement of Copyright

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S.L. Hodgetts

Thesis summary

Sex hormones exert powerful modulatory effects throughout the nervous system and influence various aspects of behaviour. For example, estrogen and progesterone have been shown to influence sex-sensitive cognitive abilities, such as verbal and visuo-spatial abilities (Hampson, 1990a, 1990b). More recently it has been suggested that estradiol can influence executive functioning abilities, such as cognitive control, working memory and selective attention (Colzato et al., 2012; Hampson, 1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002). Sex hormones have also been shown to affect functional brain organisation, in particular, cerebral lateralisation. Cerebral lateralisation is a fundamental principle of functional brain organisation, referring to the asymmetrical representation of a specific cognitive process in a particular cerebral hemisphere. For example, the left hemisphere is typically dominant for language, while the right hemisphere is dominant for visuo-spatial processes in the healthy brain (Broca, 1861; Hellige, 1993; Kimura, 1967). While men typically demonstrate pronounced, stable patterns of lateralisation, women are assumed to be less lateralised and demonstrate a higher level of intra- and inter-individual variation in the degree of lateralisation (e.g., Bibawi et al, 1995; Cowell et al., 2011; Hampson, 1990a, 1990b; Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Hjelmervik et al., 2012; Wadnerkar et al., 2008; Weis et al., 2008).

The present thesis focuses on the influence of estrogen (particularly estradiol) and progesterone on cerebral lateralisation, functional connectivity, and cognition in naturally cycling women. Young, naturally cycling women, free of hormonal contraceptives, were tested during specific phases of their menstrual cycles across a series of behavioural studies and a

resting state functional magnetic resonance imaging study. Hormone levels (estradiol and progesterone) were directly measured in each study.

The results showed that while both cerebral lateralisation and executive functioning could be modulated by sex hormones, such effects may be smaller and more specific than previously suggested. Firstly, while estradiol (and progesterone) influenced language lateralisation, this effect was dependent on the degree of asymmetry produced by the task used. Specifically, a task that yields a large degree of asymmetry (presumably due to strong bottom-up effects) is likely to mask any sex hormonal effect on other processes underpinning lateralisation, such as interhemispheric inhibition. Secondly, and similarly, the effects of estradiol on executive function and cognitive control were smaller and more specific than previously demonstrated. As such, it was argued that estradiol effects on cognition are likely dependent upon individual differences in neurophysiology, such as those that underpin different levels of schizotypy. Finally, the rs-fMRI findings demonstrate that functional connectivity in the DMN fluctuates according to different phases of the menstrual cycle, while connectivity in the auditory network is stable. Taken together, the findings presented here highlight the extensive effects of sex hormones on the brain, and on behaviours beyond those related to sexual reproduction. Furthermore, they suggest that sex hormonal effects are more complex than previously hypothesised, underpinned by their capacity to interact with task demands, other hormones, and individual differences in neurophysiology.

Chapter 1

Introduction

Sex differences in specific cognitive abilities have been extensively documented (Halpern, 2000; Kimura, 1992; Maccoby & Jacklin, 1974). While general consensus suggests that there is much overlap in cognitive performance between the sexes (e.g. McKeever, 1995), several meta-analyses have revealed that women outperform men in tests of verbal ability, perceptual speed and fine motor skill, while men excel in tests of visuo-spatial ability (such as mental rotation) and mathematical ability (Hampson, 2002). Critically, sex differences occur in cognitive functions characterised by cerebral lateralisation. That is, women excel in tasks predominantly underpinned by the left hemisphere (LH), while men excel in tasks predominantly underpinned by the right hemisphere (RH) (Halpern, 2000).

Consequently, sex is one of the most frequently investigated factors with respect to individual differences in lateralisation (Hausmann & Bayer, 2010). Sex differences in lateralisation have been reported in tasks related to language (Hausmann et al., 1998; Shaywitz et al., 1995), spatial ability (Chiarello et al., 1989; Corballis & Sidey, 1993; Hausmann & Güntürkün, 2000), and face recognition (Borod et al., 1983, Rizzolatti & Buchtel, 1977). While contradictions exist (e.g. Ashton & McFarland, 1991; Sommer et al, 2004), these studies suggest that women show a reduced degree of lateralisation (increased bilaterality), relative to men.

A large body evidence suggests that the distinct hormonal profiles of men and women are key to the generation and maintenance of such sex differences in lateralisation and cognition. However, sex hormone levels are not stable in women. Instead, they fluctuate both across the lifespan (e.g. menopause) and across shorter time intervals (e.g. the menstrual cycle). As such, menstrual cycle related hormone fluctuations may underpin the larger degree of inter- and intra-individual variation in women.

Sex hormonal effects on the brain

There are three main groups of sex hormones: estrogens, progestins, and androgens. The human principle derivatives are estradiol, progesterone, and testosterone, respectively. Due to their lipophilicity, sex steroids can cross the blood-brain barrier, despite being synthesised primarily by the gonads (e.g. testes, ovaries) and adrenal glands (Rupprecht, 2003). However, there is increasing evidence that sex hormones can be synthesised locally in specific brain regions (e.g. hippocampus, prefrontal cortex; Luine, 2014; Rupprecht, 2003).

The synthesis of sex hormones involves the conversion of cholesterol into pregnenolone. As the main precursor of all sex steroid hormones, pregnenolone is then converted via specific enzymes into other sex hormones such as progesterone, testosterone and dihydrotestosterone (Bayer & Hausmann, 2011a; Rupprecht, 2003). Testosterone is converted into estradiol by aromatase. While all three classes of hormone are present in men and women, their relative concentrations differ significantly between the sexes. While the predominant sex hormone in men is testosterone, the predominant and most potent sex steroids in women are 17β-estradiol and progesterone. In women, the circulating levels of estradiol and progesterone fluctuate across the monthly menstrual cycle, until the onset of menopause when levels of both hormones drop (Hussain et al., 2014).

Sex hormones can exert numerous effects throughout the central nervous system (CNS; McEwen & Alves, 1999; Hussain et al., 2014). Such effects can be differentiated into those that are slow in onset and long in duration (genomic effects), and those that are rapid in onset and short in duration (non-genomic effects). Genomic effects occur because, as steroid hormones, sex hormones are fat soluble and can easily pass through the lipid layer of the cell membrane. Estrogens, for example, can pass through the cell membrane and bind to the intracellular, nuclear estrogen receptors (ERs). Further evidence has revealed a number of

additional, rapid non-genomic mechanisms of estrogen effects through membrane receptors (Hussain et al., 2014; McEwen & Alves, 1999). This range of mechanisms provides the molecular basis for a wide range of sex hormone effects on brain activity and functional brain organisation.

Organising and activating effects of sex hormones

Sex hormonal effects on the brain are broadly categorised as either organising or activating effects. Organising effects result from interactions between hormones and genes, and occur primarily during early ontogenesis and puberty. These effects result in permanent sex differences in brain structure. Activating effects are the result of hormonal fluctuations that occur throughout life and, in contrast to organising effects, are transient and reflect dynamic changes in functional brain organisation (for a review, see Cohen-Bendahan, et al., 2005). Although this distinction is less clear than initially proposed (Arnold & Breedlove, 1985), it has proven a valuable heuristic to the investigation of the relationship between hormones, the brain, and behaviour (Hausmann & Bayer, 2010).

Organising effects are maximal during certain sensitive periods. The precise sensitive periods for organising effects are not known, however, it is generally accepted that gestation weeks 8-24 are a key period, although increasing evidence suggests additional sensitive periods exist (Cohen-Bendahan et al., 2005). The importance of both androgens and estrogens in early development has previously been highlighted by numerous studies in clinical populations affected by atypical hormonal environments in childhood (see section ‘Organising effects of sex hormones on lateralisation’, p.14 for further details).

Activating effects refer to the transient effects of fluctuations in sex hormone levels on brain activity, functional brain organisation, and cognitive function (Luine, 2014). To investigate the activating effects of sex hormones (i.e. estradiol and progesterone), a large

number of studies have taken advantage of the endogenous fluctuations in hormone levels that occur in young women during the menstrual cycle (Wisniewski, 1998).

The menstrual cycle is a recurring reproductive cycle, characterised by hormonal fluctuations and physiological changes in the ovaries and uterus. Each cycle begins with menstruation, and lasts approximately 28 days. The cycle can be divided into several phases, each characterised by a different hormonal profile (Figure 1).

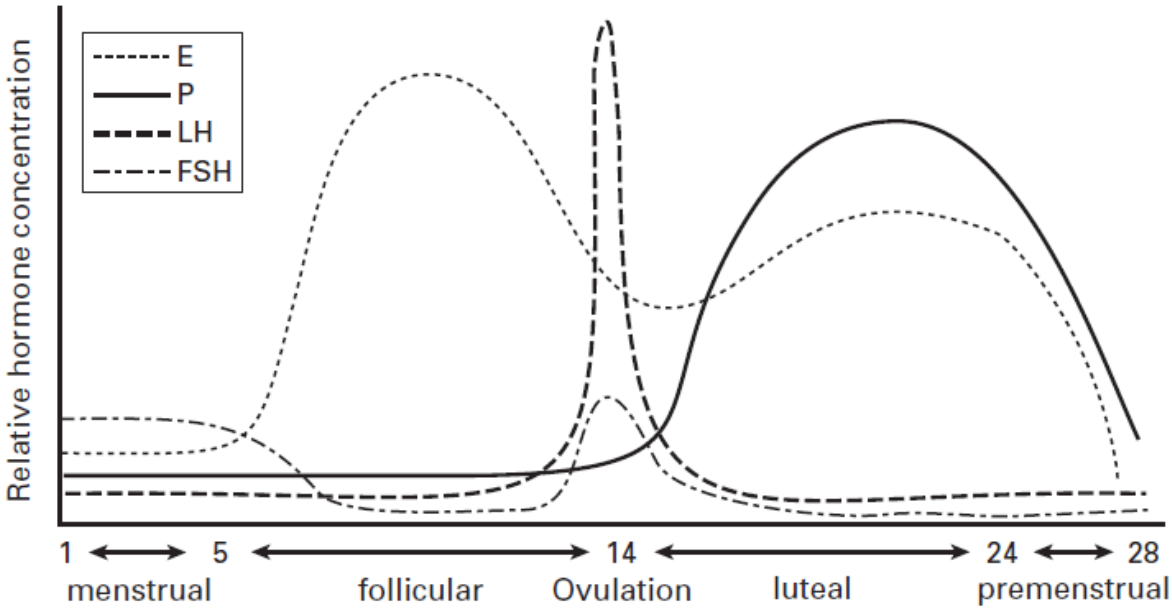

Figure 1. Fluctuations in estradiol (E), progesterone (P), luetenising hormone (LH), and follicle stimulating hormone (FSH) across a 28-day menstrual cycle (adapted from Hausmann & Bayer, 2010).

Throughout the menstrual phase (cycle days 1-5), circulating levels of estradiol and progesterone are low. At cycle day 6, estradiol begins to increase, reaching a peak just prior to ovulation; progesterone levels remain low throughout this phase (the follicular phase, cycle days 6-12). Ovulation typically occurs around cycle day 14, following the secretion of luteinising hormone. At this point, estradiol levels drop slightly. Following ovulation, the cells surrounding the egg undergo luteinisation. During this phase, estradiol and progesterone are

secreted by the luteinised cells and estradiol levels reach a second, smaller peak while progesterone levels reach their maximum (luteal phase, cycle day 22). Estradiol and progesterone levels both fall rapidly (premenstrual phase, cycle days 24 – 28) before a new cycle begins.

Sex hormones and cognition

Sex hormones have been shown to influence performance of sex sensitive cognitive abilities, such as visuo-spatial processing (Hampson, 1990a, 1990b; Hausmann et al., 2000). However, estrogen (particularly estradiol) has also been shown to affect cognitions mediated by the prefrontal cortex (PFC), such as executive functioning (Keenan et al., 2001). Executive functioning is an umbrella term that refers to the range of cognitive processes that allow us to exert cognitive control over our behaviour. Such cognitive control processes include set–shifting, response inhibition, working memory, selective attention, and behavioural monitoring (Keenan et al., 2001; Maki & Sundermann, 2009; Miller & Cummings, 2007).

Estrogen and the prefrontal cortex

A number of physiological studies, both in humans and non-human primates, have shown that estrogen receptors are present in the PFC. For example, (Wang et al., 2010) demonstrated that estrogen receptor alpha (ERα) was present in excitatory synapses dorsolateral PFC of female rhesus monkeys. Moreover, the density of these receptors was positively correlated with working memory ability in a delayed response task. Similarly, in a large post-mortem study Montague et al. (2008) revealed ERα in rhesus monkey dorsolateral PFC, rat medial PFC and, critically, human dorsolateral PFC. Additionally, in a human post-mortem study, Bixo et al. (1995) demonstrated that the concentration of estradiol in frontal cortex is higher compared to other cortical regions, such as temporal cortex and cingulate cortex. Still further studies have used animal models to investigate the direct effect of estradiol

administration on PFC morphology. For example, Hao et al. (2006) demonstrated that ovariectomised rhesus monkeys who received post-surgical estradiol treatment showed greater neuronal spine density in the PFC, as compared to those who received a placebo (see also Hao et al., 2007).

Estrogen and cognitive control processes

A number of menstrual cycle studies have demonstrated the enhancing influence of estrogen on cognitive control (Colzato et al., 2012; Hampson, 1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002). Rosenberg and Park (2002) demonstrated that verbal working memory ability fluctuated across the cycle, with participants' best performance occurring during high estradiol phases. However, this study did not include any direct hormone measurements (see also Craig et al., 2007). Using the dichotic listening paradigm (see 'Lateralisation and cognitive control demands' section, p.24 for task details), Hjelmervik et al. (2012) demonstrated that top-down cognitive control improved during the high-estradiol follicular phase, and this was directly associated with an increase in estradiol levels compared to the menstrual phase. Hampson and Morley (2013) investigated estradiol effects on working memory by comparing performance between groups of women with naturally differing levels of estradiol. In this study, women were classified as high/low in estradiol via a post-hoc median split based on saliva assays. It was found that women with relatively high levels of estradiol committed significantly fewer errors in a spatial working memory task. Similarly, Colzato et al. (2012) demonstrated that inhibitory control varies across the menstrual cycle, with women in the high–estradiol follicular phase exhibiting better inhibitory control relative to the menstrual and the luteal phases (but see Colzato et al., 2010). Moreover, in a study of post-menopausal hormone (replacement) therapy (HT)-naïve women, Wolf and Kirschbaum (2002) demonstrated that higher endogenous estradiol was associated with less interference in the Stroop task, indicative of better inhibitory control.

Due to the link between aging, the menopause, and cognitive decline (Henderson, 2008), the majority of evidence suggesting that estradiol can improve executive functioning has been conducted in post-menopausal women receiving hormone replacement therapy. Indeed, it has been suggested that it is particularly frontally mediated functions that show decline following menopause (Fuh et al., 2006; Thilers et al., 2010). Following a systematic review, Maki and Sundermann (2009) concluded that estradiol therapy has a beneficial effect on several cognitive control processes, including working memory (Duff & Hampson, 2001), problem solving (Erickson et al., 2007) and source memory (Wegesin & Stern, 2007). Similarly, Krug et al. (2006) demonstrated that a single dose of estradiol was sufficient to improve response inhibition in post-menopausal women.

In addition to these behavioural studies, evidence for an enhancing effect of estrogen therapy on PFC functioning and cognitive control processes has been found in neuroimaging studies. Joffe et al. (2006) conducted a randomised, double-blind, placebo-controlled fMRI study of estradiol effects on prefrontal cognitive functioning in 52 peri-/post-menopausal women using a battery of executive function tasks. Behaviourally, the enhancing effect of estradiol was restricted to an improvement in response inhibition only. However, the fMRI data revealed increased activation in several frontal cortical regions associated with cognitive control, including inferior frontal gyrus, dorsolateral PFC and posterior parietal regions. Subsequently, the authors conclude that estradiol therapy increases the "functional capacity" (p. 418) of the PFC, via the recruitment of additional frontal regions, leading to improvements in executive functioning.

Critically, the enhancing effect of estradiol on executive functions is inconsistent (Colzato & Hommel, 2014). For example, a high level of estradiol during the follicular phase has been associated with impaired response inhibition in a stop-signal reaction time task, as compared to both the luteal and the menstrual phases (Colzato et al., 2010). This is in direct

contrast to the enhancing effect of estradiol on response inhibition demonstrated by Colzato et al. (2012). Additional studies have linked high levels of estradiol to detriments in working memory (Gasbarri et al., 2008) and increased susceptibility to interference in the Stroop task (Hatta & Nagaya, 2009). Moreover, a recent study reported no effect of cycle-related estradiol fluctuations on a range of tasks requiring cognitive control, including working memory and verbal learning (Mihalj et al., 2014).

In light of these inconsistencies, it has recently been suggested that the effect of estradiol on cognition is dependent on individual differences in baseline dopaminergic function (Colzato & Hommel, 2014). Dopaminergic effects on cognition tasks follow an "inverted-U" function, such that performance improves with medium dopamine levels, and deteriorates with high/low levels. Given that estradiol is associated with increased dopamine turnover rates, Colzato and Hommel (2014) speculate that participants with low baseline dopamine levels, and thus poor cognitive performance, might benefit from high levels of estradiol and concurrent increases in dopamine. In contrast, those with high baseline dopamine levels, and good cognitive performance, would experience detrimental effects with high estradiol levels, as dopamine increases beyond an optimal point. A study by Jacobs and D'Esposito (2011) supports this notion. In this study, the authors demonstrated an interactive effect of baseline dopamine levels (indexed by variation associated with the catechol-O-methyltransferase $Val^{158}Met$ genotype) and menstrual cycle phase on a working memory task. Specifically, women with low baseline dopamine exhibited poor working memory during the menstrual phase (low estradiol), but improved during the follicular phase (high estradiol). In contrast, participants with high baseline dopamine demonstrated the opposite pattern; good performance when estradiol was low, and impairments when estradiol was high. Taken together, these findings suggest that while estradiol can have an enhancing effect on executive functioning and cognitive control abilities, this effect is subject to individual differences in neurophysiology.

Sex hormones and lateralisation

Organising effects of sex hormones on lateralisation

As previously mentioned, organising effects of sex hormones are typically investigated in clinical populations affected by atypical hormonal conditions during gestation or childhood. One such condition is congenital adrenal hyperplasia (CAH), a genetic condition that, in both males and females, is characterised by an underproduction of cortisol and a consequential overproduction of androgens, including testosterone. While contradictions exist (Helleday, 1994; Mathews et al., 2004), several studies in CAH patients have suggested a role for androgens in lateralisation (e.g. handedness; Kelso et al., 2000; language: Tirosh et al., 1993). For example, using a dichotic listening task, Tirosh et al. (1993) demonstrated that language lateralisation was significantly increased, particularly in female CAH patients, compared to healthy controls.

Additional clinical studies suggest that estrogen can influence lateralisation during early development (Hines & Shipley, 1984). In a behavioural study, Hines and Shipley (1984) examined language lateralisation in women exposed to diethylstilbesterol (DES) during gestation. Diethylstilbesterol is a synthetic estrogen, administered to pregnant women to lower risk of miscarriage. These authors showed that language lateralisation was significantly increased in the offspring of DES-exposed women, compared to their unexposed sisters. Although contradictions exist (e.g. Smith & Hines, 2000), this finding suggests that high levels of prenatal estradiol may play a defeminising role in male development (Hausmann & Bayer, 2010).

Lateralisation across the menstrual cycle

There is now a large body of evidence demonstrating that lateralisation fluctuates across the menstrual cycle (Alexander et al., 2002; Altemus et al., 1989; Bayer & Hausmann, 2012; Bibawi et al., 1995; Cowell et al., 2011; Hampson, 1990a, 1990b; Hausmann & Güntürkün, 1999; Hausmann & Güntürkün, 2000; Heister et al., 1989; Hjelmervik et al., 2012; McCourt et al., 1997; Mead & Hampson, 1996; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008; Weekes & Zaidel, 1996; Weis et al., 2008). However, the literature is inconsistent with respect to the direction of the laterality change and, subsequently, the mechanisms underlying the effects.

Several studies using lateralised tasks such as verbal dichotic listening (Cowell et al., 2011; Wadnerkar et al., 2008; Hampson, 1990a; Hampson, 1990b; Sanders & Wenmoth, 1998, Weekes & Zaidel, 1996) and spatial bisection (McCourt et al., 1997) have shown that lateralisation increases during high-hormone phases as compared to low-hormone phases. However, other studies have demonstrated reductions in lateralisation in high-hormone phases, relative to low-hormone phases using similar tasks, including verbal dichotic listening (Alexander et al., 2002; Altemus et al., 1989; Mead & Hampson, 1996); music dichotic listening (Sanders & Wenmoth, 1998); line bisection (Hausmann, 2005; Hausmann et al., 2002), lexical decision (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), figural comparison (Weis et al., 2011; Hausmann & Güntürkün, 2000) word matching (Weis et al., 2008) and face perception (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

In light of these inconsistencies, a number of potential mechanisms underlying cycle effects on lateralisation have been proposed. One suggestion is that sex hormones selectively influence activity of a specific hemisphere, although there is debate regarding which one. For example, in a visual-half field paradigm, Bibawi et al. (1995) presented naturally cycling women with images of chairs, presented in pairs (one to the left, and one to the right visual

field). Participants were then required to identify which chairs had been presented from a 12-item array. Results showed that during the high-hormone luteal phase, women correctly identified more chairs presented to the right visual field than the left, indicative of a left hemispheric advantage. However, during the low-hormone menstrual phase, no hemispheric advantage was found. Subsequently, the authors concluded that sex hormones selectively activate the left hemisphere. Using two dichotic listening paradigms (language and music, lateralised to the left and right hemispheres, respectively), Sanders and Wenmoth (1998) demonstrated greater language lateralisation during the luteal phase compared to the menstrual phase, but a greater asymmetry for music during the menstrual phase. Thus, these authors concluded that right hemispheric activity was selectively suppressed during high-hormone cycle phases.

Critically, several studies (e.g. Wadnerkar et al., 2008; Sanders & Wenmoth, 1998; Weekes & Zaidel, 1996; Bibawi et al., 1995; McCourt et al., 1997) did not objectively verify participants' reported cycle phase by directly measuring hormone levels. Such measures are critical for menstrual cycle research, as evidence suggests that a significant proportion of menstrual cycles in young women aged 20-24 years (approx. 40%, Metcalf & Mackenzie, 1981) are non-ovulatory. Thus, these women may not experience the expected fluctuations of estradiol and/or progesterone. Indeed, many studies that did include hormone measures report a high rate of post-hoc participant exclusion on account of their hormone levels not falling into the expected ranges for each cycle phase (e.g., up to 46% participants were excluded in Gordon et al., 1986). As such, if some participants were tested just before or after the expected peaks in estradiol and progesterone levels, there would be greater variability in the degree of lateralisation across participants.

Hausmann and Güntürkün (2000) conducted a study of lateralisation across the menstrual cycle that did include direct hormone measurements. In this study, normally cycling women

completed left-hemispheric (word matching) and right-hemispheric (figural comparison, face discrimination) tasks, during both the low-hormone menstrual phase and the high-progesterone luteal phase. Cycle phase was verified by salivary hormone assays. In addition, a sample of men and a sample of post-menopausal women were tested at corresponding time intervals. The authors identified an interaction between cycle phase and lateralisation in all tasks, indicative of a general reduction in lateralisation during the high-progesterone luteal phase. In contrast, lateralisation was stable across time in post-menopausal women and men. A second study replicated these findings with the same tasks (Hausmann et al., 2002). In this study, normally cycling women were tested 15 times at three-day intervals. This allowed for a longitudinal analysis of the relationship between sex hormones and lateralisation for longer than one menstrual cycle, as well as a cross-sectional analysis. For the figural comparison task both analyses indicated a significant relationship between progesterone and reduced lateralisation, resulting from an enhanced performance of the sub-dominant left hemisphere.

As these studies demonstrated reduced lateralisation for both left- and right-hemispheric tasks when levels of progesterone were high, it was suggested that sex hormones were not selectively influencing the activity of a particular hemisphere. Instead, Hausmann and Güntürkün (2000) proposed that hormones affect lateralisation by modulating interhemispheric interaction, a physiological process that affects both hemispheres. This mechanism is based on the assumption that the lateralisation of a cognitive process, to either hemisphere, arises due to inhibition of the non-dominant hemisphere by the dominant hemisphere (i.e. interhemispheric inhibition) via the corpus callosum (Chiarello & Maxfield, 1996; Cook, 1984). Specifically, Hausmann and Güntürkün (2000) argued that although cortico-cortical transmission is primarily excitatory, interhemispheric inhibition occurs because the lasting effect of callosal activity is inhibition of the contralateral hemisphere (Innocenti, 1980). This inhibition occurs because the majority of callosal projections terminate on pyramidal neurons, which

subsequently activate GABAergic interneurons (Toyama & Matsunami, 1976). Moreover, it has been shown that callosal projections may also terminate directly on GABAergic interneurons (Conti & Manzoni, 1994). Both of these mechanisms would result in widespread inhibition of homotopic regions of the non-dominant hemisphere by the dominant hemisphere (Kawaguchi, 1992).

In the *hypothesis of progesterone-mediated hemispheric decoupling* (see Fig. 2), Hausmann and Güntürkün (2000) proposed that high levels of progesterone during the luteal phase leads to a reduction of interhemispheric inhibition. This leads, in turn, to a functional decoupling of the two hemispheres and a reduction in lateralisation. Specifically, it was proposed that progesterone, and metabolites such as allopregnanolone, can reduce interhemispheric inhibition by suppressing the excitatory neural response to glutamate and increasing the inhibitory neural response to GABA (Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Hausmann & Bayer, 2010). This view was supported by a number of physiological studies, demonstrating that progesterone suppresses the excitatory response of neurons to glutamate, primarily via non-NMDA receptors, while also increasing the inhibitory response of neurons to GABA (Smith et al., 1987a, 1987b). Still further studies have shown that similar effects are obtained with combined estradiol and progesterone administration (Smith et al., 1987b). Thus, it was proposed that high levels of progesterone in the luteal phase might lead to a transient reduction in interhemispheric inhibition, and in turn, a reduction in lateralisation (Hausman & Güntürkün, 2000; Hausmann et al., 2002).

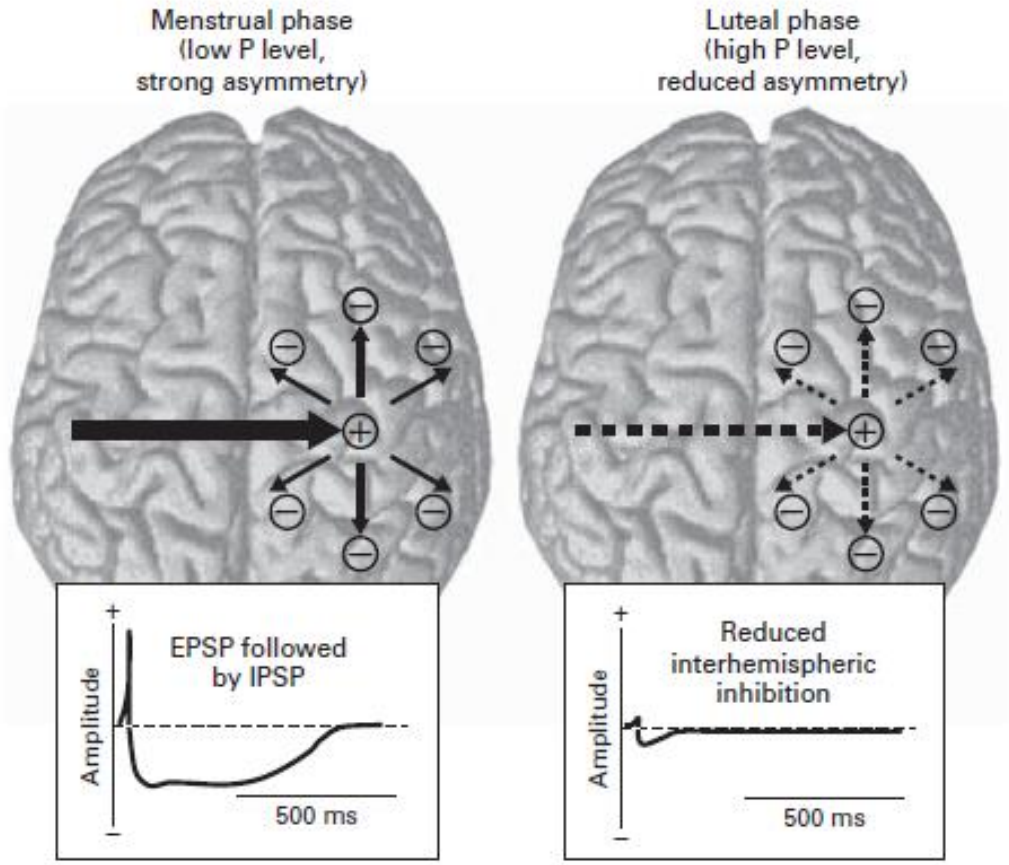

Figure 2. Graphical depiction of interhemispheric inhibition (left) and the progesterone-mediated hemispheric decoupling hypothesis (right). Although cortico-cortical transmission (left of figure, indicated by the solid black arrow) is primarily excitatory, the longer lasting effect appears to be inhibition of the contralateral hemisphere. This is probably due to callosal fibres terminating on pyramidal neurons, and consequently activating inhibitory interneurons. These inhibitory, GABAergic neurons then induce widespread inhibition in homotopic regions of the contralateral hemisphere. The hypothesis of progesterone-mediated hemispheric decoupling (right of figure) suggests that progesterone reduces cortico-cortical transmission during the luteal phase by supressing the excitatory neural response to glutamate, and increasing the inhibitory response to GABA (Hausmann & Gunturkun, 2000; Hausmann et al., 2002). This results in a transient, functional decoupling of the two hemispheres, as the dominant hemisphere can no longer inhibit the subdominant hemisphere. This in turn leads to a temporary reduction in lateralisation. (P, progesterone; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential) (Adapted from Hausmann & Bayer, 2010).

Weis et al. (2008) reported evidence for the notion that sex hormones can influence inter-hemispheric inhibition and lateralisation. In this study, naturally cycling women underwent functional magnetic resonance imaging (fMRI) while completing a word-matching task, identical to that used by Hausmann and Güntürkün (2000). All women were tested during both the low-hormone menstrual phase and the high-estradiol follicular phase. A control group of males were tested at corresponding time intervals. Functional connectivity was assessed using psychophysical interaction analysis (PPI) to determine the inhibitory influence of the dominant left hemisphere on the non-dominant right hemisphere. Behaviourally, a significant left-hemispheric advantage was found in the menstrual phase, which was reduced in the follicular phase. In addition, PPI analysis revealed that the inhibitory influence of the left hemisphere over the right hemisphere fluctuated according to estradiol levels. Specifically, high levels of estradiol during the follicular phase were associated with reduced interhemispheric inhibition, and in turn, reduced lateralisation. In contrast, no change in lateralisation or interhemispheric inhibition was found in the male controls. Moreover, no significant difference was found when activity in left inferior frontal gyrus (a region critical to the word-matching task) was directly compared between the menstrual and follicular phases.

The finding that high levels of sex hormones can reduce interhemispheric inhibition, leading to reduced lateralisation during high-hormone cycle phases, is in line with the mechanism proposed by Hausmann and Güntürkün (2000). However, Weis et al. (2008) showed that it was estradiol that was associated with a reduction in interhemispheric inhibition, not progesterone. Given that estradiol and progesterone have partly opposing effects on GABA and glutamate receptors (Smith et al., 1987a, 1987b), it may be argued that these hormones work at different stages in the range of neurophysiological processes underpinning lateralisation, or that both hormones are precursors of the active steroid hormone (Weis et al.,

2008; Hausmann & Bayer, 2010). An alternative explanation is that estradiol and progesterone have similar effects on lateralisation, but respectively in the follicular and luteal phase.

This notion was previously investigated in a transcranial magnetic stimulation (TMS) study (Hausmann et al., 2006). In this study, TMS was applied to the left motor cortex to evoke a transient suppression of voluntary muscle activity in the ipsilateral hand muscle. This so-called ipsilateral silent period (iSP) is mediated by callosal fibres, and is presumed to reflect transcallosal inhibition with shorter iSPs indicating less inhibition. It was found that iSP duration varied across the menstrual cycle, with the shortest iSPs being found in the follicular phase. More importantly, regression analyses revealed that short iSPs during the follicular phase were significantly related to estradiol, while short iSPs during the luteal phase were significantly related to progesterone. This finding suggests that although estradiol and progesterone exact mainly opposing effects of GABA and glutamate receptors, high levels of each hormone can have similar effects on interhemispheric inhibition during the follicular and luteal phases, respectively.

In recent years, research into sex hormonal effects in the brain has expanded to investigate other aspects of functional connectivity, such as intrahemispheric connectivity (Weis et al., 2011). For example, using a figural comparison task, Weis et al. (2011) investigated whether reductions in lateralisation for this task were similar to those seen for the verbal task (Weis et al., 2008). Behaviourally, women demonstrated reduced lateralisation during the luteal phase. In addition, fMRI data revealed cycle-phase related changes in functional connectivity *within* the task dominant hemisphere. Specifically, activation of right-hemispheric networks was reduced during the luteal phase, as compared to both the menstrual and the follicular phase. In addition, PPI analysis revealed cycle-related changes in functional connectivity, such that stronger functional connectivity between a right temporal seed region (fusiform gyrus) and heterotopic regions of the left hemisphere (e.g. precuneus, postcentral gyrus, inferior parietal

lobule) was found during the luteal phase. Consequently, the authors suggest that sex hormones modulate not only interhemispheric inhibition between homotopic areas (Weis et al., 2008) but can also influence intrahemispheric integration, and interhemispheric connectivity between heterotopic brain regions (Weis et al., 2011).

Sex hormones and resting state connectivity

In light of evidence showing that sex hormones can affect task-related functional connectivity, recent research has begun to investigate sex hormonal effects on functional connectivity in the brain at rest. In the absence of a specific cognitive task, the brain exhibits a pattern of low-frequency oscillations in the BOLD signal (approx. 0.01-0.1Hz, Damoiseaux et al., 2006). Biswal et al. (1995) were the first to demonstrate the "resting state" fMRI (rs-fMRI) approach, revealing temporally correlated time courses of low frequency oscillations within the sensory motor cortex. Subsequent research using rs-fMRI has identified a number of networks that are spatially comparable to task-related activations (Damoiseaux et al., 2006), such as executive function (Laird et al., 2011; Seeley et al., 2007), language (Laird et al., 2011; Tie et al., 2014) and memory (Laird et al., 2011; Vincent et al., 2006) resting state networks. Given that functional connectivity is susceptible to endogenous hormone fluctuations across the menstrual cycle (Weis et al., 2008; Weis et al., 2011), sex hormones may also be capable of influencing resting state connectivity. This is a critical issue, as it suggests that sex hormone effects on task performance and functional brain organisation may not be due to an effect on task-related brain activity, but reflective of their effect on task-independent intrinsic connectivity.

Four recent studies have investigated the effect of cycle-related hormone fluctuations on resting state network connectivity but with inconsistent results (Arélin et al., 2015; De Bondt et al., 2015; Hjelmervik et al., 2014; Petersen et al., 2014). Using a between-subjects design,

Petersen et al. (2014) investigated resting state functional connectivity under different hormonal conditions, across the menstrual cycle in normally cycling women, and in oral contraceptive pill users. Normally cycling women were either in the menstrual phase (termed early follicular by the authors) or the luteal phase. This study reported increased functional connectivity between the right anterior cingulate cortex (ACC) and the executive control network, and reduced functional connectivity between the left angular gyrus and the anterior DMN during the luteal as compared to the menstrual phase. In contrast, Hjelmervik et al. (2014) investigated four fronto-parietal cognitive control networks, using a repeated measures design. No cycle-related effect on functional connectivity was found. Similarly, De Bondt et al. (2015) did not find any effect of sex hormones in fronto-parietal networks (termed 'executive control networks' by the authors). However, analysis of the DMN revealed an increase in functional connectivity in the luteal phase, relative to the follicular phase, between the cuneus and the network. Arélin et al. (2015) conducted 32 resting state scans in a single subject across four menstrual cycles. Results showed that high progesterone levels were associated with increased connectivity of the dorsolateral PFC and the sensorimotor cortex to the resting state network. Further analysis revealed that high progesterone levels were associated with higher functional connectivity between right dorsolateral prefrontal cortex bilateral sensorimotor cortex, and the hippocampus, as well as between the left dorsolateral PFC and bilateral hippocampi.

Lateralisation and post-menopausal hormone therapy

The activating effect of sex hormones on cerebral lateralisation has also been investigated in studies involving hormone administration. This approach involves investigating lateralisation in post-menopausal women undergoing HT (Bayer & Erdmann, 2008; Bayer & Hausmann, 2009a, 2009b; for reviews see Bayer & Hausmann, 2011a, 2011b). Bayer and Erdmann (2008) demonstrated an increase in left-hemispheric performance for verbal processing in women undergoing estrogen-only HT. In a further study, Bayer and Hausmann

(2009b) demonstrated reduced right-hemispheric lateralisation for a figure-matching task in post-menopausal women undergoing HT (both estrogen-only and estrogen-gestagen combination), which was significantly related to estradiol levels. Consequently, it was concluded that HT enhances left hemispheric verbal processing at the expense of visuo-spatial processing.

Lateralisation and cognitive control demands

Given that sex hormones, particularly estradiol, have been shown to influence cerebral lateralisation and cognitive control processes, it is not surprising that recent research has investigated the possible relationship between these three factors. Indeed, Hjelmervik et al. (2012) investigated this notion using a forced-attention dichotic listening paradigm. This task is a robust tool used to provide a behavioural measure of language lateralisation. It involves the simultaneous presentation of two, different auditory stimuli, separately to the left and right ear. Participants are required to report which stimuli they heard the most clearly. Typically, in healthy right-handed adults, this task reveals a bias favouring the right ear, indicative of left-hemispheric language lateralisation. However, the so-called right-ear advantage (REA) can be modulated by instructing participants to selectively attend to and report from either the left or the right ear specifically. In contrast to the non-forced condition, the forced-left condition requires a high level of cognitive control, as participants must override their bias towards the dominant right ear. In this study, naturally cycling women completed the task three times across the cycle. A cycle–related effect was found only in the forced-left condition. In this condition, women demonstrated a greater left-ear advantage during the high-estradiol follicular phase, as compared to both the menstrual and luteal phases. The authors interpreted this finding as evidence of an active role of estradiol on cognitive control, and not on language lateralisation.

Furthermore, the authors suggested that this finding indicates that cognitive control demands may be a potential confounder in studies of lateralisation, especially as lateralised

tasks may vary in terms of the amount of cognitive control they require. For example, while word-matching tasks require working memory processes, lexical decision tasks do not. Moreover, while studies using word matching typically show cycle effects on language lateralisation (Hausmann and Güntürkün, 2000; Weis et al., 2008, respectively), lexical decision studies often report no cycle effects (Chiarello et al., 1989; Heister et al., 1989; Weekes and Zaidel, 1996; see Chapter 2 for further discussion of these studies). Together with the findings from Hjelmervik et al. (2012), this suggests that cognitive control demands may be a possible confound when investigating language lateralisation (and lateralisation more generally).

Aim of the present thesis

The aim of the present thesis is to investigate hormonal effects on cerebral lateralisation, executive functioning, and resting state functional connectivity, in healthy, naturally cycling women.

The first section of this thesis (Chapters 2 and 3) will address open questions regarding which of the several processes underpinning lateralisation are affected by sex hormones. Specifically, these studies aimed to determine whether hormonal effects on lateralisation are driven by the effect of estradiol on top-down factors (such as cognitive control), or bottom-up (stimulus driven) factors. The two studies presented here used three dichotic listening paradigms, in which participants were required to listen to pairs of auditory stimuli, presented dichotically, under three attention conditions. In the "non-forced" conditions, participants were required to state which of the two stimuli they heard most clearly. In two forced-attention conditions, participants were required to selectively attend to, and report from either the left or the right ear. Normally cycling women were tested once, in a between-subjects design (High vs. Low estradiol, and menstrual cycle phases), and saliva sampling was used to objectively measure sex hormone levels.

The second section of this thesis (Chapters 4 and 5) aims to investigate the modulatory properties of sex hormones on cognitive control in a clinically relevant context. These chapters investigate whether sex hormones, particularly estradiol, can have an enhancing effect on meta-memory, a specific cognitive control process that is known to be affected by schizophrenia. This was done using a non-clinical model of schizophrenia (i.e., schizotypal personality traits), and a non-clinical analogue of delusion symptoms (i.e., false memories). Across these two studies, normally cycling women undertook three tests of meta-memory ability, designed to produce false memories, and assess how confident participants are in such memories. Again, a between-subjects design was used, and saliva sampling allowed for the objective measurement of sex hormone levels.

Finally, Chapter 6 presents an investigation of sex and sex hormonal effects on resting state functional connectivity. For this study, a group of naturally cycling women were scanned during three different phases of the menstrual cycle. In addition, a control group of males was scanned at comparable time points. Functional connectivity in both a cognitive and a sensory resting state network was compared between males and females, and across the menstrual cycle in females. As in previous chapters, saliva samples were obtained to objectively measure sex hormone levels.

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Chapter 2

Sex hormones affect language lateralisation but not cognitive control in normally cycling women

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Abstract

Natural fluctuations of sex hormones during the menstrual cycle have been shown to modulate language lateralisation. Using the dichotic listening (DL) paradigm, a well-established measurement of language lateralisation, several studies revealed that the left hemispheric language dominance was stronger when levels of estradiol were high. A recent study (Hjelmervik et al., 2012) showed, however, that high levels of follicular estradiol increased lateralisation only in a condition that required participants to cognitively control (top-down) the stimulus-driven (bottom-up) response. This finding suggested that sex hormones modulate lateralisation only if cognitive control demands are high. The present study investigated language lateralisation in 73 normally cycling women under three attention conditions that differed in cognitive control demands. Saliva estradiol and progesterone levels were determined by luminescence immunoassays. Women were allocated to a high or low estradiol group. The results showed a reduced language lateralisation when estradiol and progesterone levels were high. The effect was independent of the attention condition indicating that estradiol marginally affected cognitive control. The findings might suggest that high levels of estradiol especially reduce the stimulus-driven (bottom-up) aspect of lateralisation rather than top-down cognitive control.

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Introduction

Natural fluctuations of sex hormones, such as those that occur during the menstrual cycle, have been shown to exert a modulating effect on functional brain organisation. Cerebral lateralisation refers to the differential involvement of the left or the right hemispheres in specific cognitive process such as language, spatial abilities or face discrimination (Hellige, 1993). Although it is well-known that the left hemisphere is dominant for most language processes (Broca, 1861; Kimura, 1967), it has previously been suggested that sex differences exist with respect to the degree of language lateralisation, with males demonstrating a greater language lateralisation for specific tasks compared to women (e.g. Jaeger et al., 1998; Shaywitz et al., 1995); although results are inconsistent (e.g. Sommer et al., 2004, Voyer, 2011).

One reason for this inconsistency is that while language lateralisation is comparatively stable in men, it fluctuates within relatively short time periods across the menstrual cycle in women (Hampson, 1990a, 1990b; Rode et al., 1995; Weis et al., 2008). Indeed, a number of neuropsychological studies, across different modalities and cognitive processes (both verbal and non-verbal), have demonstrated reduced lateralisation during cycle phases associated with high levels of estradiol (i.e. follicular phase, Holländer et al., 2005; Weis et al., 2008) or high levels of both estradiol and progesterone (i.e. luteal phase, Hausmann, 2005; Hausmann et al., 2002; Hausmann and Güntürkün, 2000; Rode et al., 1995), and greater lateralisation (similar to men) during the low-hormone menstrual phase. Thus, the presence of a sex difference in lateralisation may partly be dependent on women's hormonal status at time of testing (see Hausmann and Bayer, 2010, for a review).

Regarding the mechanisms underlying this effect, it has been suggested that rather than selectively influencing activity in a particular hemisphere, lateralisation is influenced via modulation of a central mechanism affecting both hemispheres. Specifically, it was proposed

that lateralisation arises from interhemispheric inhibition of the non-dominant hemisphere by the dominant hemisphere (Chiarello and Maxfield, 1996; Cook, 1984). Furthermore, it has been suggested that it is especially progesterone (and its metabolites) that reduces corticocortical transmission via glutamatergic and GABAergic effects, resulting in reduced interhemispheric inhibition, and consequently reduced lateralisation (Hausmann and Güntürkün, 2000). More recent studies suggest that it is estradiol and progesterone (e.g. Hausmann et al., 2006) or estradiol alone (e.g. Hausmann, 2005; Holländer et al., 2005; Weis et al., 2008) that modulates the interhemispheric interaction between the left and right hemispheres (Hausmann et al., 2013; see Hausmann and Bayer, 2010 for a review).

Results from cycle-related studies of language lateralisation that used the dichotic listening (DL) paradigm are particularly inconsistent. The DL task is a well-established tool to investigate language lateralisation. It involves the presentation of two auditory stimuli, usually monosyllabic words (e.g. Alexander et al., 2002; Hampson, 1990a, 1990b) or consonant-vowel syllables (e.g. Cowell et al., 2011; Wadnerkar et al., 2008; Sanders and Wenmoth, 1998). One stimulus is presented to the left and the other is presented simultaneously to the right ear. Participants are required to verbally report the syllable/word they heard the most clearly. In healthy right-handed adults, this task typically reveals a bias towards stimuli presented to the right ear, indicative of left-hemispheric language lateralisation. It has recently been suggested that while there is a significant sex difference in the DL bias (i.e. males more lateralised than females), this effect is small (Hirnstein et al., 2014; Voyer, 2011). The right ear advantage (REA) results from several factors relating to the anatomy of auditory projections from the ear to the primary auditory cortex (Kimura, 1967). Firstly, although auditory information is relayed to both hemispheres via subcortical projections, contralateral projections are stronger than ipsilateral ones. Consequently, stimuli presented to right ear have direct access to the language-dominant left hemisphere. In contrast, stimuli presented to the left ear are projected to the right

hemisphere and have to be transferred, via the corpus callosum, for processing. Finally, under dichotic conditions (i.e. simultaneous stimulus presentation), the ipsilateral projections are suppressed in favour of processing contralateral stimuli (Hugdahl, 2003; Kimura, 1967; Pollmann et al., 2002, for a review see Westerhausen and Hugdahl, 2008).

In contrast to studies using visual paradigms, the majority of DL studies looking at menstrual cycle effects reported increased language lateralisation when levels of estradiol and/or progesterone are high (Cowell et al., 2011; Hampson, 1990a, 1990b; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008). However, there are also DL studies showing the opposite, a decreased REA during the luteal phase ("premenstrual week", Alexander et al., 2002; Altemus et al., 1989; midluteal phase, Mead & Hampson, 1996). Two recent DL studies did not find that the menstrual cycle affected language lateralisation (the non-forced condition in Hjelmervik et al., 2012; Can et al., 2012). These inconsistent finding of menstrual cycle effects in dichotic listening studies are summarized in Table 1.

Table 1: Studies of dichotic listening (DL) and menstrual cycle phase illustrating different methods and findings (adapted from Hausmann & Bayer, 2010).

Study	Number of participants	Mean age	Handedness	Cycle phases (cycle days)	Definition of phase	DL paradigm(s)	Main results
Alexander et al. (2002)	30	32.03 (SD = 8.9)	Right	Menstrual (1 - 7) Follicular (8 - 14) Midcycle (15 - 21) Premenstrual (22 - 28)	Day count	Verbal (rhyming nonsense syllables, rhyming monosyllabic words, negative words, positive words, neutral words).	Reduced REA during premenstrual phase compared to follicular phase across all tasks.
Altemus et al. (1989)	39	30 (range: 18-45)	Right	Follicular (6 - 12) Premenstrual (21 - 28)	Day count	Verbal (rhyming nonsense syllables, rhyming monosyllabic words, negative words, positive words, neutral words).	Reduced REA during premenstrual phase across all tasks.
Can et al. (2012)	32	25.23 (SD = 4.57)	Right	Menstrual (2 - 5) Follicular (8-11) Luteal (20-22)	Saliva assays (E, P)	Verbal (consonant-vowel).	No cycle effects.
Cowell et al. (2011)	21	25.24 (SD = 0.74)	Right	Menstrual (2 – 5) Periovulatory (8 – 11) Luteal (18 – 25)	Blood assays (E, P, LH, FSH)	Verbal (consonant-vowel).	Reduced REA during the menstrual phase.
Hampson (1990a)	45	23.7 (range: 19-39)	41 right-handed 4 non-right handed	Menstrual (3 – 5) Midluteal (18 -23)	Day count	Verbal (monosyllabic words)	Reduced REA during menstrual phase (only trend).
Hampson (1990b)	50	26.4 (range: 20-43)	43 right handed 7 non-right handed	Menstrual (3 – 5) Follicular (12 – 13)	Blood assays (E, P, LH)	Verbal (monosyllabic words)	Reduced REA during the menstrual phase
Hjelmervik et al. (2012)	15	23.47 (SD = 5.11)	Right	Menstrual (2 - 4) Follicular (8 – 12) Luteal (20 – 22)	Saliva assays (E, P)	Verbal (consonant-vowel, three forced-attention conditions).	Increased LEA during the follicular phase (forced-left condition only).
Mead & Hampson (1996)	36	23.7 (range: 20–36)	Right	Menstrual (3 – 5) Midluteal (18 – 23)	Saliva assays (E)	Verbal (emotional prosody, linguistic).	Linguistic: Reduced REA during midluteal phase (only session 1). Emotional prosody: Reduced LEA during menstrual phase.
Sanders & Wenmoth (1998)	32	24 (range: 18-37)	Right	Menstrual (3 – 5) Midluteal (20 - 22)	Day count	Verbal (consonant-vowel) Music (chord recognition)	Verbal: Reduced REA during menstrual phase. Music: Reduced LEA during midluteal phase.
Tillman (2010)	23	Mean not reported (range: 18-35	Right	Menstrual (onset of menstruation ± 1 day) Follicular (16 – 17 days prior to menstruation)	Saliva assays (E, P)	Verbal (semantic categorisation) Non-verbal (complex tones)	Reduced ERP latencies to the left hemisphere (from the right ear) during the follicular phase and to the right hemisphere (from the left ear) during the menstrual phase. No behavioural LEA/REA reported.
Wadnerkar et al. (2008)	25	22.56 (SD = 2.04)	Right	Menstrual (2 – 5) Midluteal (18 – 25)	Day count	Verbal (consonant-vowel, three attention conditions).	Reduced REA during menstrual phase (all attention conditions combined).

Right ear advantage (REA), left ear advantage (LEA), estradiol (E), progesterone (P), lutenising hormone (LH), follicular stimulating hormone (FSH), event related potential (ERP).

One critical limitation and potential explanation for these inconsistencies is that the majority of DL studies (Altemus et al., 1989; Alexander et al., 2002; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008) did not include direct hormone measurements but relied entirely on calendar methods to estimate cycle phases and the underlying estradiol and progesterone levels. Direct hormone measurements are a prerequisite for menstrual cycle research, as previous studies had to exclude large numbers of participants (up to 46%, Gordon et al., 1986) because hormone assays revealed that participants were not in the expected cycle phase. As a result, if some participants were tested just before or after the expected peak in estradiol and/or progesterone levels, the variability in the degree of lateralisation would be greater across participants.

Task instruction can also affect the REA and interact with sex and menstrual cycle effects in the DL task (Voyer and Ingram, 2005; Hjelmervik et al., 2012; Wadnerkar et al., 2008). In these studies, participants are required to selectively attend to and report from either the left or the right ear, in addition to the standard non-forced attention condition. In contrast to the non-forced condition, the forced-left condition requires top-down cognitive control, requiring participants to actively override the tendency to report stimuli presented to the dominant right ear (Hugdahl, 2003; Loberg et al., 1999; Hugdahl et al., 2009). In line with other reports of sex differences in auditory attention (Halley, 1975; Andersson and Hugdahl, 1987), Voyer and Ingram (2005) found that women had a higher number of intrusions from the uncued ear compared to men. This finding was interpreted by the authors as evidence that women experiencing greater difficulty in orienting their attention to the cued ear compared to men. Furthermore, this suggests that top-down factors could account for sex differences in the DL bias. Regarding menstrual cycle studies, while Wadnerkar et al. (2008) pooled data across all three conditions, Hjelmervik et al. (2012) found a cycle-related change only in the condition that required participants to shift attention to stimuli presented to the left ear. In this condition,

women in the follicular phase showed an increased left-ear advantage compared to both the menstrual and the luteal phase. As no menstrual cycle effect was observed in the non-forced condition, Hjelmervik et al. (2012) concluded that estradiol influences cognitive control as opposed to language lateralisation *per se*. This is in line with previous studies showing that estradiol has an enhancing effect on cognitive control in non-lateralised tasks, such as working memory, recognition memory, and response inhibition (Jacobs and D'Esposito, 2011; Keenan et al., 2001). Moreover, this indicates that the prefrontal cortex (PFC) is an important site of estrogen activity in the female brain, as has been proposed by others (Hampson and Morley, 2013; Joffe et al., 2006; Keenan et al., 2001; Wang et al., 2010). In addition, this suggests that cognitive control can be a potential confounder in studies of lateralisation.

As noted by Hjelmervik et al. (2012), lateralisation tasks may vary in the amount of cognitive control they require. For example, word-matching tasks ask participants to report whether two consecutively presented words are the same, which requires the updating component of working memory. In contrast, lexical decision tasks require participants to discriminate words from non-words; this does not require working memory. Indeed, studies using word matching typically show reduced language lateralisation during the luteal and follicular phase (Hausmann and Güntürkün, 2000; Weis et al., 2008, respectively), while lexical decision studies often report no cycle effects (Chiarello et al., 1989; Compton and Levine, 1997; Heister et al., 1989; Weekes and Zaidel, 1996). Together with the findings from Hjelmervik et al. (2012), this suggests that cognitive control demands may be a possible confound when investigating language lateralisation (and lateralisation more generally). This again may partly explain some of the aforementioned inconsistencies.

In the present study we investigated normally cycling women using three attention conditions of the Bergen DL test (Hugdahl, 1995, 2003), which is identical to the task used in Hjelmervik et al. (2012). In contrast to previous studies, we adopted a between-subjects design,

which is more conservative (Charness et al., 2012), and avoids potentially confounding carry-over effects due to the repeated measures design (e.g. Soveri et al., 2013; Hausmann and Güntürkün, 1999). Such carry-over effects were, for example, reported by Hampson (1990b) showing that cognitive performance can increase when participants are initially tested in a physiologically conducive state, compared to those who began testing in a less favourable physiological state for a particular task. Moreover, by comparing groups with high or low hormone levels (as opposed to cycle phases), we maximise the differences in estradiol (and progesterone) levels, allowing to test whether sex hormones affect language lateralisation directly, or indirectly via an estradiol effect on cognitive control. If gonadal steroid hormones affect the bottom-up process related to language lateralisation, it is predicted that estradiol and/or progesterone will reduce the DL bias across all attention conditions. However, if high levels of gonadal hormones selectively affect top-down cognitive control, estradiol-related changes are expected only in the forced-left DL condition (Hjelmervik et al., 2012).

Method

Participants

Seventy-three healthy, normally cycling women (out of 81 participants tested; see hormone assessment section for exclusion details) with a mean age of 23.00 years (*SD* = 4.86; range: 19 – 40 years) were assigned to either a High estradiol (*n* = 37) or Low estradiol (*n* = 36) group, based on saliva estradiol assays.

All women were native English speakers and right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The laterality quotient (LQ) provided by this hand preference measure is calculated as [(R – L)]/(R + L)] × 100, resulting in values between -100 and +100, indicating consistent sinistrality and dextrality respectively. The mean LQ was 88.10

(*SD* = 13.83). There were no differences in age nor handedness between the estradiol groups (all $t_{(71)} < 1.21$, ns).

All participants reported no hearing difficulties, were not pregnant and did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

Procedure

The day of testing was arranged according to participants' self-reported cycle day (days 1-4, 7-12, 15-23, corresponding to the menstrual, follicular or luteal phase; respectively). Saliva samples were collected at the beginning of the test session. Saliva estradiol was used as the findings of Hjelmervik et al. (2012) identified saliva estradiol levels as significantly related to DL laterality shifts. This method of classification is based on objective quantification of estradiol levels, as opposed to inaccurate self-reports of current menstrual cycle phases. However, varying the cycle day of testing between women ensured a maximum range of estradiol levels. The majority of women allocated to the High estradiol group were in the luteal phase according to self-reports (*n* = 23). Consequently, it was expected that the High estradiol group would also yield higher progesterone levels. The Low estradiol group was primarily comprised of participants in the self-reported menstrual (*n* = 16) or follicular (*n* = 14) phases. Given that the follicular phase is characterised by a high level of estradiol, this demonstrates cycle phase estimation (based on day counts) did not correspond with directly measured hormone levels in the present study. This suggests either that participants' estimation of their current cycle phase was inaccurate, or that the majority of participants experienced an anovulatory cycle.

To facilitate collection of saliva samples, women were asked to avoid eating, drinking, smoking and brushing teeth for 30 minutes prior to the testing session. One sample (2 × 1 ml)

was collected at the beginning of the test session. The saliva was stored at -20°C until completion of the study. Samples were assayed by an independent professional hormone laboratory with commercially available luminescence immunoassays for estradiol and progesterone. The sensitivity of the estradiol assay was 0.3 pg/ml, the sensitivity of the progesterone assay was 2.6 pg/ml. Intra-assay coefficients for estradiol and progesterone were 13.3 % and 6 %, respectively. The allocation of participants to either the High or Low estradiol groups was based on a median-split (split score: 3.4 pg/ml). Eight women were excluded from further analyses due to contamination (sample was semi-fluid and/or discoloured, suggesting blood contamination).

Table 2: Estradiol, progesterone, handedness and age (mean ± standard deviation and range) for all women in each estradiol group.

	Low estradiol (n =36) M ± SD (range)	**High estradiol (n = 37)** M ± SD (range)
Estradiol (pg/ml)	2.07 ± 0.76 (0.6 – 3.30)	5.83 ± 3.5 (3.40 – 20.30)
Progesterone (pg/ml)	77.25 ± 59.58 (20.6 – 327.5)	147.82 ± 107.04 (21.30 – 366.7)
Handedness LQ	90.04 ± 13.72 (60-100)	86.2 ± 13.87 (52.94 – 100)
Age	22.31 ± 4.49 (19 – 40)	23.68 ± 5.18 (19 – 38)

The Bergen Consonant-Vowel Dichotic Listening Test

The Bergen Consonant-Vowel Dichotic Listening Test was included as part of a larger test battery of cognitive tasks. The stimuli set was six consonant-vowel syllables (/ba/, /da/, /ga/, /ka/, /pa/, /ta/), spoken with constant intonation and intensity by an English male voice. The stimuli were presented as 30 dichotic pairs (e.g. /ba/ - /pa/), and six additional homonymic pairs (e.g. /ba/ - /ba/). The syllable duration was 400 – 450 ms with an inter-stimulus interval of 4000 ms. The stimuli were administered through a computer using Windows Media Player,

and participants listened to the stimuli through supra-aural headphones (K271, AKG Acoustics, Vienna, Austria). Participants were required to give an oral response to each trial, which was recorded by the experimenter. The 36 trials were presented three times, each time with a different randomised order of trials, totalling 108 trials. Each block of trials began with a different instruction, in line with three attention conditions. All participants began with the non-forced condition, in which they were instructed to report the sound they heard the most clearly. This was followed by the forced-right/forced-left condition, in a counterbalanced order between participants, in which participants were respectively asked to attend to and report from the right or left ear. The non-forced condition was always completed first and was not randomised between participants so as to avoid biasing participants' responses regarding the attended ear. For each condition, the percentage of correct left-ear reports and correct right-ear reports were scored separately, and used to calculate LQs using the following formula[1]: [(RE - LE)/(RE + LE) × 100]. Homonymous pairs were excluded from the analysis.

Data analysis

Non-parametric tests were used where assumptions of normality were not met. Greenhouse-Geisser adjustments were used whenever sphericity was violated.

Results

Salivary hormone concentrations

The mean saliva estradiol and progesterone concentrations are given in Table 2. Estradiol levels in the High estradiol group were significantly higher than those in the Low estradiol group, $U = 1332.0$, $p < .001$, as were progesterone levels, $U = 958.5$, $p < .001$. There was no significant

[1] For descriptive statistics of the raw ear scores, please see Appendix i.

correlation between estradiol and progesterone in either the High estradiol (r_s = .02, p = .88), or the Low estradiol group (r_s = .23, p = .18).

Dichotic listening task

The laterality quotients (Table 3) were subjected to a 3 × 2 mixed model ANOVA, with Condition (non-forced, forced-right, forced-left) as the within-subjects, and Group (High estradiol, Low estradiol) as the between-subjects factor. The significant intercept effect revealed an REA across the whole sample ($F_{(1, 71)}$ = 33.07, p <.001, η_p^2 = .32). The main effect of Condition was significant, ($F_{(1.37, 97.58)}$ = 187.83, p <.001, η_p^2 = .73). Post-hoc pairwise comparisons revealed that LQs in the forced-right condition were significantly greater than in the non-forced condition (p <.001), indicating an increased REA in the forced-right condition. Furthermore, LQs in the forced-left condition were significantly smaller (i.e. negative) than in the non-forced and forced-right conditions, indicating a shift to a LEA in the forced-left condition (both p < .001). The Condition × Group interaction was not significant ($F_{(1.37, 97.58)}$ = 3.37, p = .056, η_p^2 = .045).

Table 3. Mean LQ and standard deviations across attention conditions (non-forced, forced-right, forced-left, all conditions combined) in each group.

	Low estradiol N = 36	**High estradiol N = 37**
Non-forced	17.78 ± 18.67	11.73 ± 20.57
Forced-right	49.00 ± 20.95	39.51 ± 24.19
Forced -left	-34.53 ± 25.21	-25.24 ± 22.99
All combined	10.75 ± 11.38	8.67 ± 16.86

It is important to note that the main effect of Group on LQ was not significant, probably because of positive LQs and negative LQs being averaged across all three attention conditions,

thereby masking a general, condition-independent reduction in ear asymmetries. We therefore conducted a second analysis in which we included the absolute LQs for all conditions (see Figure 1).

The absolute LQs were subjected to a 3 × 2 mixed model ANOVA with Condition (non-forced, forced-right, forced-left) as the within-subjects factor, and Group (High estradiol, Low estradiol) as the between-subjects factor (see Figure 1). The main effect of Condition was significant ($F_{(1.53, 108.90)}$ = 36.17, p <.001, η_p^2 = .34). Post-hoc pairwise comparisons revealed that the absolute LQ in the forced-right condition was significantly greater than in both the non-forced and forced-left conditions (both p <.001). Moreover, the absolute LQ was larger in the forced-left condition than in the non-forced condition (p <.002). More importantly, and in contrast to the previous analysis, the main effect of Group was significant ($F_{(1, 71)}$ = 4.52, p <.037, η_p^2 =.06), indicating that the absolute LQ in the High estradiol group (M = 25.50, SD = 17.21) was significantly reduced as compared to the Low estradiol group (M =33.77, SD = 15.99). The Condition × Group interaction was not significant ($F_{(1.53, 108.90)}$ = 0.155, p = .80, η_p^2 .002).

It should be noted that, if absolute LQs were analysed according to a progesterone median split, neither the main effect of Cycle phase ($F_{(1, 71)}$ = .29, p =.59, η_p^2 = .004), nor the Cycle phase × Condition interaction ($F_{(1.53, 108.76)}$ = .28, p = .69, η_p^2 =*.004*) approached significance. Similarly, conducting the same analysis using estimated cycle phases based on day count (i.e. menstrual/cycle day 1-4, follicular/cycle day 7-12, luteal/cycle day 15-23) rather than using High versus Low estradiol groups, neither the main effect of Cycle phase ($F_{(2, 70)}$ = 2.77, p =.07, η_p^2 = .07), nor the Cycle phase × Condition interaction ($F_{(3.04, 106.27)}$ = .59, p = .62, η_p^2 =*.02*) reached significance. Subjecting the standard LQs to the same analysis revealed similar results for both the main effect of Cycle phase ($F_{(2, 70)}$ = .06, p = .94, η_p^2 =.002) and the Cycle phase × Condition interaction ($F_{(2.76, 96.47)}$ = 2.59, p = .06, η_p^2=*.07*). However, as

previously stated, it is important to note that participants' cycle phase estimation did not correspond with salivary hormone levels. Therefore, drawing conclusions based on cycle phase is highly problematic in the current study.

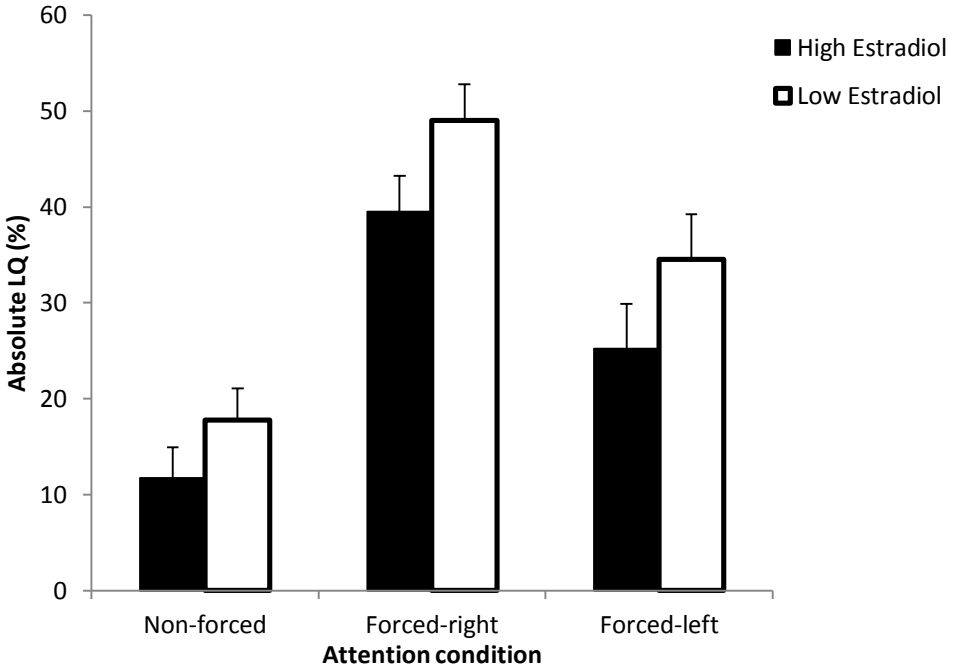

Figure 1. Mean absolute laterality quotient (LQ) and standard error means according to estradiol group (high, low) for each attention condition. LQs represent the degree of ear advantage by the dominant versus non-dominant ear.

Relationship between absolute laterality quotients and sex hormones

Spearman's correlation revealed a small but significant relationship between mean absolute LQs (all attention conditions combined) and estradiol levels (r_s = -.24, p = .04) but not with progesterone levels (r_s = -.15, p = .19). However, due to the significantly reduced absolute DL biases across all conditions in women with higher levels of estradiol, and the possibility that estradiol and progesterone may have interactive effects on language lateralisation, we conducted a moderated multiple regression to investigate the relationship between sex hormone levels and absolute LQs. The mean absolute LQ (across all three attention conditions) was used

as dependent variable. To avoid multicolinearity, independent (predictor) variables were centered. The interaction variable was calculated as the product of estradiol and progesterone (both centered). The regression analysis did not revealed a significant model, $F_{(3, 69)} = 1.94$, $p = .13$, $R^2 = .078$. The only predictor that approached significance was estradiol ($\beta = -.269$ $p = .06$). Progesterone and the estradiol × progesterone interaction did not approach significance ($\beta = -.113$, $p = .34$, $\beta = -.222$, $p = .12$, respectively). Together with the significant Spearman's correlation, the trend effect in the regression suggests a weak relationship between high levels of estradiol and reduced language lateralisation across all conditions (see Figure 2). Notably, participants with the highest estradiol levels were in the follicular cycle phase, according to self-report.

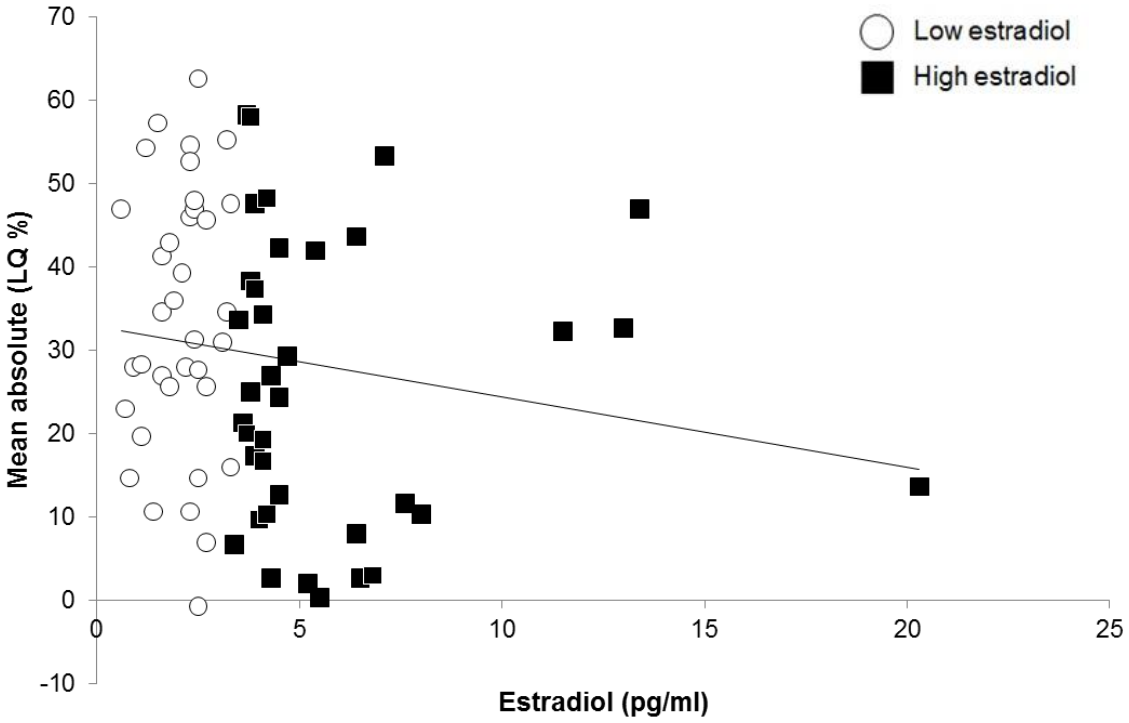

Figure 2. Scatterplot of the relationship between the estradiol levels and the mean absolute LQs in the dichotic listening task averaged across all attention conditions. Black squares represent Participants of the High estradiol group; white circle represent participants of the Low estradiol group. NB: Graph depicts non-centered estradiol levels, centering was used in the moderated multiple regression analysis.

Discussion

The present study demonstrated a reduction in the absolute DL bias across all attention conditions for the High estradiol group, compared to the Low estradiol group. This suggests that high levels of estradiol are related to reduced language lateralisation as measured with the DL paradigm. However, both groups differed significantly in estradiol *and* progesterone levels. The correlation analysis suggested that the absolute DL bias was reduced with increasing estradiol levels. Further analysis using moderated multiple regression basically confirmed that estradiol alone was the best predictor (although only approaching significance) for the reduced absolute DL bias. Although the estradiol × progesterone interaction was also negatively related to the DL bias, this effect was not significant. These results suggest that high levels of estradiol reduce language lateralisation. These findings are fundamentally different to Hjelmervik et al. (2012) who found a positive relationship between estradiol levels and the DL bias in the forced-left condition only. This finding was interpreted by the authors as an estradiol-related improvement in cognitive control, as opposed to an effect on language lateralisation per se.

It is noteworthy that Hjelmervik et al. (2012) and the present study investigated normally-cycling women with the identical Bergen DL paradigm, though stimuli were spoken by a native Norwegian (Hjelmervik et al.) or English (present study) male speaker. However, there are some important differences between the studies that might partly account for the conflicting findings. Firstly, the current study revealed consistently larger DL biases across all conditions. Specifically, the mean REAs in the non-forced and forced-right conditions (averaged across High/Low estradiol groups) in the current study are about twice as large as those in Hjelmervik et al. (2012). The difference in average LEAs in the forced-left condition between studies is even larger (greater in the current study). The comparatively small ear advantages in Hjelmervik et al. (2012) may partly explain why there was no further reduction in DL biases when hormone levels were high. Secondly, women in the present study showed higher mean

concentrations and also a larger range of estradiol levels, possibly partly due to the larger sample size in the current study. This, together with the fact that the present study compared extreme groups (low/high estradiol), instead of testing women during different cycle phases, might have promoted a hormone effect on language lateralisation. Third, it should be noted that participants in the present study with high estradiol levels also had high progesterone levels. This is different to the hormone profiles of the follicular phase reported by Hjelmervik et al. (2012) and suggests that while estradiol alone improves cognitive control, the effect on language lateralisation may also depend on progesterone levels. Finally, Hjelmervik et al. (2012) adopted a within-subjects design, which is potentially subject to carry-over effects (e.g. Hampson, 1990b; Hausmann and Güntürkün, 1999; Charness et al., 2012), as opposed to the between-subject design in the present study. As mentioned above, the forced-left condition requires cognitive control - the ability to override a stimulus-driven response in favour of an instruction-driven one (i.e. top—down process). Given that all participants in Hjelmervik et al. (2012) performed the DL task three times, during different cycle phases, it is possible that repeated testing enhanced participants' ability to cognitively control the stimulus-driven bottom-up process. Indeed, as previously discussed, Hampson (1990b) demonstrated that cognitive performance can increase when participants are initially tested in a physiologically conducive state, compared to those who began testing in a less favourable physiological state for a particular task (see also Mead & Hampson, 1996). Thus, in Hjelmervik et al. (2012), high levels of estradiol during the follicular phase may have provided a physiologically conducive state which may have promoted the LEA in the more demanding forced-left condition.

Although all previous DL studies counterbalanced the cycle phase in which participants were tested, an interactive effect of repeated testing and hormonal state on language lateralisation cannot be ruled out, as shown by participants initially tested during high-hormone cycle phases (Hampson 1990a, b; Mead & Hampson, 1996). To determine the stability of the

laterality bias, some studies repeatedly tested male or postmenopausal female controls at comparable time points (e.g. Hausmann and Güntürkün, 2000; Hjelmervik et al., 2012; Hjelmervik et al., 2014; Bayer et al., 2008; Weis et al., 2011) because their hormone levels are relatively stable. However, it has been argued that these procedures may not completely rule out carry-over effects (Hausmann and Güntürkün, 1999). Therefore, the present study is not subject to this potential confound.

In contrast to the majority of studies investigating menstrual cycle effects on language lateralisation as measured by DL (Cowell et al., 2011; Wadnerkar et al., 2008; Sanders and Wenmoth, 1998), the current study found a reduction in lateralisation when estradiol and progesterone levels were high, regardless of the attention condition. As different attention conditions were used, resulting in either LEAs or REAs, it is unlikely that the general reduction in language lateralisation is due to sex hormones selectively affecting one hemisphere. It is also rather speculative that estradiol and/or progesterone modulated the efficacy of the ipsilateral/contralateral projections from the non-dominant/dominant ear to the right/left auditory cortices because sex hormonal effects on subcortical auditory pathways are not known (Al-Mana et al, 2008). We are therefore inclined to believe that the observed reduction in condition-specific DL biases occurred on the cortical level.

It has recently been proposed (see Hausmann and Bayer, 2010, for review) that sex hormones modulate lateralisation through their neuromodulatory effects on interhemispheric inhibition. It was originally proposed that progesterone reduces lateralisation by suppressing the excitatory responses of neurons to glutamate and increasing their response to GABA, leading to a ‘decoupling’ of the hemispheres by reducing corticocortical transmission and interhemispheric inhibition (Hausmann and Güntürkün, 2000). Subsequent research has provided evidence that estradiol may also modulate interhemispheric interaction and, in turn, lateralisation (Hausmann et al., 2013, Weis et al., 2008; Weis et al., 2011; Hausmann et al.,

2006; Holländer et al., 2005). In line with this hypothesis, the reduced REA found in the non-forced and forced-right condition in the High estradiol group may be explained by a reduction of inhibition of the subdominant right hemisphere by the dominant left. This would facilitate right hemisphere processing of stimuli presented to the left ear. Similarly, the reduced LEA in the forced-left condition for the High estradiol group may be viewed as a reduction of inhibition from the right hemisphere over the left hemisphere, which subsequently facilitates left hemisphere processing of stimuli presented to the right ear, which would consequently reduce the LEA.

Further analysis of the absolute LQs indicated that the reduction in the DL bias was mainly underpinned by estradiol. Although progesterone levels were also high in the high estradiol group, progesterone alone and the interaction between estradiol and progesterone did not predict the DL bias. Therefore, the results of the present study directly contribute to the debate concerning which sex hormone, estradiol and/or progesterone, drives menstrual cycle-related effects on language lateralisation (Hausmann and Bayer, 2010; Weis et al., 2008). Indeed, although estradiol and progesterone exact opposing influences on glutamatergic and GABAergic receptors, a transcranial magnetic stimulation study (Hausmann et al., 2006) revealed that estradiol and progesterone can have similar attenuating effects on interhemispheric inhibition, during the follicular and luteal phases, respectively. In addition, Smith et al. (1987) showed that combining estradiol with a high dose of progesterone leads to a decrease in excitatory neural responses to glutamate, similar to the effect of progesterone alone. Although progesterone was not directly linked to language lateralisation in the present study, it is important to note that the high estradiol group also had high progesterone levels. Thus, we cannot rule out that high levels of estradiol might have reduced the interhemispheric inhibition in combination with progesterone, as was previously suggested (see Hausmann & Bayer, 2010; Weis & Hausmann, 2010 for reviews), thereby decreasing DL bias across all

attention conditions in the present study. However, the exact mechanism underlying the interactive effect of estradiol and progesterone on absolute LQs remains an open question.

In conclusion, in contrast to previous studies (Hjelmervik et al., 2012; Cowell et al., 2011; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008), the present study revealed a reduced lateralisation in women with high levels of estradiol and progesterone across all DL conditions. This suggests that the proposed estradiol-related improvements in cognitive control may be smaller than previously reported (Hjelmervik et al., 2012). The present findings rather support the notion that sex hormones affect language lateralisation directly, probably via a modulation of stimulus-driven bottom-up processes and interhemispheric inhibition. This finding also suggests that reduced lateralisation is related to high levels of estradiol. The present study highlights the need to consider interactions between sex hormones when investigating lateralisation across the menstrual cycle. Moreover, with respect to sex differences in language lateralisation, the present study provides further evidence to suggest that while women are less lateralised compared to men, the degree of sex difference in (language) lateralisation may partly dependent on women's hormonal state during the menstrual cycle phase. Finally, the present study suggests that the top-down and bottom-up aspects of lateralisation can be differently affected by hormonal fluctuations across the menstrual cycle. This might be an additional factor that may account for some of the inconsistencies in the literature on sex differences in the functional organisation of the brain.

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Chapter 3

Estradiol-related variations in top-down and bottom-up processes of cerebral lateralisation

Abstract

Natural fluctuations of sex hormones during the menstrual cycle have been shown to modulate cerebral lateralisation in dichotic listening tasks. Two recent studies have presented contradictory notions regarding the mechanism of this effect. Specifically, while Hjelmervik et al. (2012) suggested that estradiol affects lateralisation by enhancing top-down processes, such as cognitive control, Hodgetts et al. (2015) suggested that the effect was due to estradiol-related variations in bottom-up aspects of lateralisation. Using two well-established left- and right-lateralised dichotic listening tasks (Hugdahl, 1995, 2003; Grimshaw et al., 2003; 2009), with two new forced-attention conditions, the present study was designed to differentiate between these two ideas. Fifty-two naturally cycling women underwent both an emotional prosody and a linguistic dichotic listening task. Saliva estradiol and progesterone levels were determined by luminescence immunoassays. Women were tested once, during either the menstrual, follicular or luteal cycle phase. The results showed that sex hormones did not affect language lateralisation, which may be due to the larger degree of lateralisation yielded by the task, compared to that shown by Hodgetts et al. (2015). In the emotional prosody task, high levels of estradiol were marginally associated with a reduction in cognitive control; while the language task yielded no cycle effects for either top-down, or bottom-up processes. In sum, the current study revealed weak support for the idea that estradiol affects top-down control of lateralisation, as measured with dichotic listening tasks. Given that the task employed in the present study seemed less cognitively demanding than that used previously, it is suggested that estradiol-related inter- and intra-individual variations in lateralisation are small when task demands are low.

Introduction

Sex hormones, such as estradiol and progesterone, have been shown to influence functional brain organisation. In particular, cerebral lateralisation (i.e., the differential involvement of the left or the right hemispheres in specific cognitive process) is sensitive to the fluctuations in estradiol and progesterone that occur naturally across the menstrual cycle. While lateralisation is stable in men, it fluctuates within relatively short time periods across the menstrual cycle in women (for a review, see Hausmann & Bayer, 2010). Indeed, a number of neuropsychological studies, across different modalities and cognitive processes, have demonstrated reduced lateralisation during cycle phases associated with high levels of estradiol during the follicular phase (e.g., Holländer et al., 2005; Weis et al., 2008) or high levels of both estradiol and progesterone during the luteal phase (e.g. Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Hausmann, 2005; Rode et al., 1995; Alexander et al., 2002; Altemus et al., 1989; Mead & Hampson, 1996) as compared to greater lateralisation during the low-hormone menstrual phase in these studies.

The dichotic listening (DL) paradigm is commonly used to investigate language lateralisation (Hugdahl, 1995, 2003; Hugdahl et al., 2009). The paradigm involves the presentation of two auditory stimuli, usually monosyllabic words (e.g. Alexander et al., 2002; Hampson, 1990a, 1990b) or consonant-vowel syllables (e.g. Cowell et al., 2011; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008). One stimulus is presented to the left ear, and the other is presented simultaneously to the right ear. Participants are required to report the syllable/word they heard the most clearly, either verbally or by button press. In healthy right-handed adults, this task typically reveals a bias towards stimuli presented to the right ear, indicative of left-hemispheric language lateralisation. The so-called right ear advantage (REA) results from several factors relating to the anatomy of auditory projections from the ear to the primary auditory cortex (Kimura, 1967). Firstly, although auditory information is relayed to

both hemispheres via subcortical projections, contralateral projections are stronger than ipsilateral ones. Therefore, when both ears are stimulated simultaneously, the ipsilateral projections are suppressed in favour of processing contralateral stimuli (Hugdahl, 2003; Kimura, 1967; Pollmann et al., 2002, for a review see Westerhausen and Hugdahl, 2008). Stimuli presented to right ear have direct access to the language-dominant left hemisphere. In contrast, stimuli presented to the left ear are projected to the right hemisphere and have to be transferred via the corpus callosum for processing.

Several studies have used the DL task to investigate language lateralisation across the cycle, yielding inconsistent results. While many studies have demonstrated increased language lateralisation when levels of estradiol and/or progesterone are high (Cowell et al., 2011; Hampson, 1990a, 1990b; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008), others have shown the opposite, a decreased REA during the luteal phase ("premenstrual week", Alexander et al., 2002; Altemus, et al., 1989; midluteal phase, Mead & Hampson, 1996). Moreover, two recent DL studies did not find that the menstrual cycle affected language lateralisation; the non-forced condition in Hjelmervik et al. (2012) and Can et al. (2012) (see Hodgetts et al. 2015, Chapter 2 for a review).

Task instruction can also affect the REA and interact with menstrual cycle effects in the DL task (Hjelmervik et al., 2012; Wadnerkar et al., 2008; Hodgetts, Weis, & Hausmann, 2015). In these studies, participants are required to selectively attend to and report from either the left or the right ear, in addition to the standard non-forced attention condition in which participants are not required to allocate attention to either the left or right ear. In contrast to the non-forced attention condition, the forced-left condition requires top-down cognitive control, requiring participants to actively override the tendency to report stimuli presented to the dominant right ear (Hugdahl, 2003; Loberg et al., 1999; Hugdahl et al., 2009). While Wadnerkar et al. (2008) pooled data across all three conditions, Hjelmervik et al. (2012) found a cycle-related change

only in the condition that required participants to shift attention to stimuli presented to the left ear. In this condition, women in the high-estradiol follicular phase showed an increased left-ear advantage compared to both the menstrual and the luteal phase. As no menstrual cycle effect was observed in the non-forced condition, Hjelmervik et al. (2012) concluded that estradiol influences cognitive control as opposed to language lateralisation *per se*.

A recent study by Hodgetts et al. (2015, Chapter 2) aimed to replicate this finding. In this study, the DL task was used in a between-subjects design. Naturally cycling women were tested only once, with all three forced-attention conditions, and hormone levels (assessed via saliva assays) were used *post-hoc* to classify women as either high or low in estradiol. In contrast to Hjelmervik et al. (2012), this study demonstrated reduced lateralisation in women with relatively high estradiol levels across all attention conditions and regardless of cognitive control demands. Consequently, it was concluded that sex hormones, and particularly estradiol, reduced the stimulus-driven, bottom-up aspect of lateralisation, while top-down cognitive control was unaffected. Given that different attention conditions were used, Hodgetts et al. (2015) argued that the observed effect was unlikely to be due to sex hormones selectively influencing one hemisphere. Moreover, it was argued that it is unlikely that sex hormones influenced the efficacy of the subcortical projections that give rise to the DL biases, as sex hormonal effects on subcortical auditory pathways are not known (Al-Mana et al., 2008). Instead, it was proposed that the observed reduction in DL biases occurred on the cortical level, perhaps by sex hormones modulating lateralisation via their neuromodulatory effects on interhemispheric inhibition (Hausmann, 2010; Hausmann & Bayer, 2010; Weis & Hausmann, 2010).

The *hypothesis of progesterone-mediated decoupling* originally proposed that high levels of progesterone reduced lateralisation by suppressing the excitatory responses of neurons to glutamate and increasing their response to GABA. In turn, this would result in a ‘decoupling’

of the hemispheres by reducing corticocortical transmission and interhemispheric inhibition (Hausmann & Güntürkün, 2000). This model was later revised, in light of evidence that estradiol may also modulate interhemispheric interaction and, in turn, lateralisation (Hausmann et al., 2013; Weis et al., 2008; Weis et al, 2011; Hausmann et al., 2006; Holländer et al., 2005). In line with this hypothesis, Hodgetts et al. (2015) argued that the reduced REA found in women with high estradiol levels during the non-forced and forced-right conditions may be explained by a reduction of inhibition of the subdominant right hemisphere by the dominant left. This would facilitate right hemisphere processing of stimuli presented to the left ear. Similarly, the reduced LEA in the forced-left condition may be viewed as a reduction of inhibition from the right hemisphere over the left hemisphere, which subsequently facilitates left hemisphere processing of stimuli presented to the right ear, which would consequently reduce the LEA.

Given that interhemispheric inhibition is a universal process that should affect lateralisation generally, it follows that high estradiol levels should also reduce lateralisation for tasks related to the right hemisphere. Thus, the present study aims to extend these findings of Hodgetts et al. (2015) using a different DL paradigm. The present study used a DL paradigm that includes both a linguistic and an emotional prosody task. Like the DL tasks used in previous studies (Cowell et al., 2011; Hjelmervik et al., 2012; Hodgetts et al., 2015; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008), this task involves the simultaneous presentation of two different words, one to the left and one to the right ear. However, unlike the tasks used in the aforementioned studies, the words presented to participants in the present study also differ in emotional prosody. Thus, participants may be asked to listen to the stimuli and respond to a specific word in the linguistic task, or they may be asked to respond to a specific emotional tone in the emotional prosody task. These tasks have been shown to produce a REA and a LEA, respectively on account of left hemispheric specialisation for language processing, and right

hemispheric specialisation for emotion processing (Bryden & MacRae, 1988; Grimshaw et al., 2003; 2009; Najt et al., 2011). In addition, similar to Hjelmervik et al. (2012) and Hodgetts et al. (2015), the present study incorporated a cognitive control (top-down) element into both the linguistic and the emotional prosody task, by implementing two forced-attention conditions and asking participants to respond only to targets presented to the left or right ear. This experiment was designed to differentiate between two contradicting ideas claiming that estradiol can affect lateralisation by modulating (improving) the top-down (Hjelmervik et al., 2012) or bottom-up aspects of cerebral lateralisation (Hodgetts et al., 2015). If estradiol affects the bottom-up aspects of lateralisation, reduced DL biases should be found in both tasks, regardless of the forced attention condition, when estradiol levels are high. In contrast, if estradiol affects cognitive control, increased DL biases should be found in the forced-left and forced-right conditions of the linguistic and emotional tasks, respectively.

Method

Participants

Fifty-two healthy, normally cycling women (out of 55 tested; see Hormone Assessment section for exclusion details) with a mean age of 25.15 years (*SD* = 6.60, range: 19-41 years) were tested either during the menstrual (cycle days 2 - 5), follicular (cycle days 8 - 12), or luteal cycle phase (cycle days 20 - 22). All participants were native English speakers and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The laterality quotient (LQ) provided by this hand preference measure is calculated as [(R – L) / (R + L)] × 100, resulting in values between –100 and +100, indicating consistent sinistrality and dextrality, respectively. The mean LQ was 78.79 (*SD* = 19.82). There was no difference in age ($F_{(2, 49)}$ = 0.49, p = .62) or handedness ($F_{(2, 49)}$ = 0.12, p = .88) between the groups. Mean age and handedness are given in Table 1.

Table 1. Estradiol, progesterone, handedness and age (mean ± standard deviation and range) for all women in each cycle phase.

	Menstrual (n = 17) M ± SD (range)	**Follicular (n = 18)** M ± SD (range)	**Luteal (n = 17)** M ± SD (range)
Estradiol (pg/ml)	2.73 ± 2.45 (0.30 – 8.80)	4.45 ± 3.66 (1.40 – 16.80)	4.42 ± 4.34 (0.40 – 20.10)
Progesterone (pg/ml)	101.41 ± 34.00 (46.00 – 177.00)	130.89 ± 62.77 (52.00 – 283.00)	281.94 ±109.96 (73.00 – 510)
Handedness LQ	77.02 ± 23.91 (20.00 – 100)	78.87 ± 18.53 (37.50 – 100)	80.46 ± 17.59 (47.37 – 100)
Age	24.29 ± 6.27 (19.00 – 41.00)	26.39 ± 6.42 (20.00 – 39.00)	24.71 ± 7.29 (19.00 – 41.00)

All participants reported no current/previous psychiatric or neurological illness. Participants were not pregnant and did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

Hormone assays

Two saliva samples were collected during each session, one before the dichotic listening tasks, and one after (2 × 1 ml). To facilitate the collection of the samples, all participants were asked to avoid eating, drinking, smoking, chewing gum or brushing their teeth for 30 minutes prior to the test session. The saliva was stored at -20°C until completion of the study. Samples were assayed by an independent, professional hormone laboratory with commercially available luminescence immunoassays for estradiol and progesterone. The analysis was completed on an average amount of the two samples. The sensitivity of the estradiol assay was 0.3 pg/ml, the sensitivity of the progesterone was 2.6 pg/ml. Intra-assay coefficients for estradiol and progesterone were 13.3% and 6%, respectively.

Three women were excluded from further analyses due to progesterone levels exceeding the range of the assay (> 1000 pg/ml), or contamination by blood.

The linguistic and prosodic dichotic listening task

The DL task consisted of a linguistic (target word identification) and a prosodic task (target emotional tone identification). The stimulus set for both tasks consisted for four, two-syllable words: "bower", "dower", "power" and "tower" spoken in angry, happy, sad and neutral tones of voices by a New Zealand male voice (Grimshaw et al., 2003; 2009). The stimuli were presented in blocks of 144 trials, consisting of all possible pairings of words and emotions, with the constraint that a different word/emotion combination was presented to each ear on each trial (e.g. "bower" in a sad tone to the left ear, "tower" in a happy tone to the right ear).

Participants were instructed to monitor for either word target or to a tone of voice target, and provide a single response on each trial. During the linguistic task, participants were asked to monitor for the word "bower", while in the prosodic task participants were required to monitor for the sad tone of voice. These particular targets were chosen so as to elicit the strongest REA and LEAs respectively (Grimshaw et al., 2003). Participants were required to indicate, as quickly and accurately as possible, whether the target was present or absent. Responses were given by pressing one of two keyboard buttons (one for "target present", one for "target absent"). During each block and for both tasks, the target was present in 50% of trials (25% in the left ear, 25% in the right ear). The stimuli were delivered using E-Prime (Psychology Tools Inc., Pittsburgh, PA) on a laptop (Lenovo 4233, Morrisville, NC) and supra-aural headphones (K271, AKG Acoustics, Vienna, Austria).

For each task, participants completed three blocks (see Figure 1). Each block of trials began with a different instruction, in line with the three different attention conditions. All participants began with the non-forced attention condition, the order of the forced-attention conditions was randomised and counterbalanced between participants. In the non-forced condition, participants were asked to monitor for the target, and indicate whether the target was

present or absent on each trial, regardless of which ear the target was presented to. In the forced-attention conditions, participants were asked to monitor for the target being presented to a particular ear, and respond with "present" only if the target was presented to that ear. If the target was presented to the non-attended ear, they were to ignore it (i.e. respond "absent"). Task order (linguistic or prosodic task first) and was randomised and counterbalanced between participants. Orientation of the headphones (normal or reversed) was also randomised and counterbalanced between participants, in order to control for potential mechanical differences between channels. In addition, participants used both hands to respond, with half beginning each block with their right hand and half beginning each block with their left hand, with all participants swapping hand half way through each block.

For each task and each condition, the number of times the target (word/emotion) was identified in each ear was recorded. This was used to calculate both the directional laterality quotients, using the following formula: [(RE - LE) ÷ (RE + LE) × 100], and the absolute laterality quotients, based on dominant (D) ÷ non-dominant (ND) ears, using the following formula[2]: [(D – ND) ÷ (D + ND) × 100].

[2] For descriptive statistics of the raw ear scores, please see Appendix i.

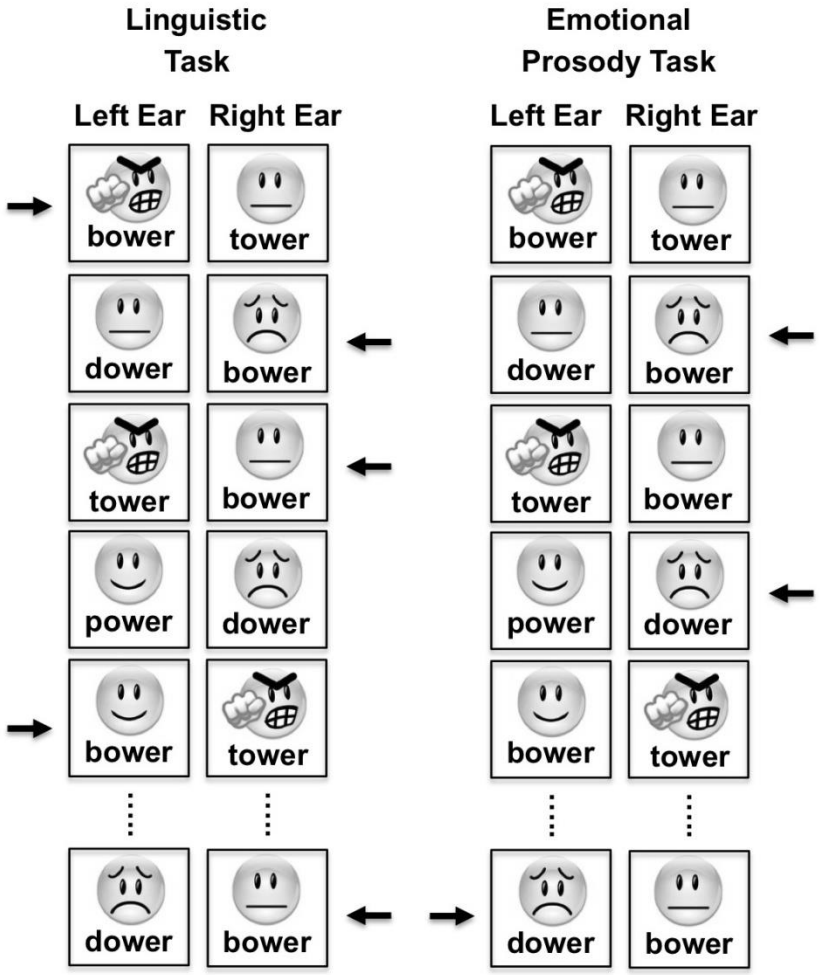

Figure 1. Schematic figures of the linguistic and emotional prosody dichotic listening tasks. In the non-forced condition, participants are required to pay attention to both ears at the same time and indicate, via button press, whether the target word/tone was present or absent. This condition was always presented first to avoid biasing participants' responses in the forced attention conditions. In the forced attention conditions, participants were required to selectively attend to, and report from, either the left or the right ear. The order of the forced attention conditions was counterbalanced between participants. The arrows indicate correct responses across trials for each task (i.e., target word ('bower') in the linguistic task and target emotion ('sad intonation') in the emotional prosody task).

Data analysis

Non-parametric tests were used where assumptions of normality were not met. Greenhouse-Geisser adjustments were used whenever sphericity was violated.

Results

Salivary hormone concentrations

The mean saliva estradiol and progesterone levels are given in Table 1. Although mean estradiol levels were numerically higher in the follicular and luteal groups compared to the menstrual group, there was no main effect of Cycle Phase on estradiol levels ($F_{(2, 49)} = 1.29$, $p = .28$). A significant effect of Cycle Phase was found for progesterone ($F_{(2, 49)} = 28.15$, $p < .001$), and post-hoc tests (Bonferroni) revealed significantly higher progesterone levels in the luteal group as compared to both the menstrual and follicular groups (both $p < .001$). There was no difference in progesterone levels between the menstrual and follicular groups ($p = .761$).

Dichotic listening tasks

The laterality quotients were subjected to a 2 × 3 × 3 mixed model ANOVA, with Task (emotional, linguistic) and Condition (non-forced, forced-right, forced-left) as the within-subjects factors, and Cycle Phase (menstrual, follicular, luteal) as the between-subjects factor. The main effect of Task was significant ($F_{(1, 49)} = 46.42$, $p < .001$, $\eta_p^2 = .49$), indicating an expected overall REA (mean LQ ± *SD*: 13.88 ± 14.02) for the linguistic task and LEA (-4.29 ± 11.02) for the prosody task. The main effect of Condition was also significant ($F_{(1.75, 85.66)} = 988.77$, $p < .001$, $\eta_p^2 = .95$), indicating a greater REA (83.66 ± 17.02) in the forced-right condition, as compared to both the non-forced and forced-left conditions across both tasks (both $p < .001$), and a significant LEA in the forced-left condition, as compared to both the non-forced and forced-right conditions across both tasks (both $p < .001$). Moreover, there was a significant Task × Condition interaction ($F_{(1.69, 82.69)} = 13.42$, $p < .001$, $\eta_p^2 = .22$). This

interaction as followed up by two repeated measures ANOVAs, one for each task, with condition as the within-subjects factor. For both the emotional and the linguistic tasks, the main effect of Condition was significant ($F_{(1.47, 74.73)}$ = 421.38, p < .001, η_p^2 = .89; $F_{(2, 102)}$ = 904.55, p < .001; η_p^2 = .95 respectively). Mean laterality quotients for each condition in each task are depicted in Figure 2. For both tasks, post-hoc tests (Bonferroni) revealed significant differences between the non-forced and forced-right conditions, the non-forced and forced-left conditions, and the forced-right and forced-left conditions (all p < .001). Taken together, the interaction shows that, across cycle phases, participants were able to shift their attention according to the task instructions in both tasks. There was no Condition × Cycle Phase interaction, no Task × Cycle Phase interaction, and no between-subjects effect of Cycle Phase (all F < 0.67, p > .59)

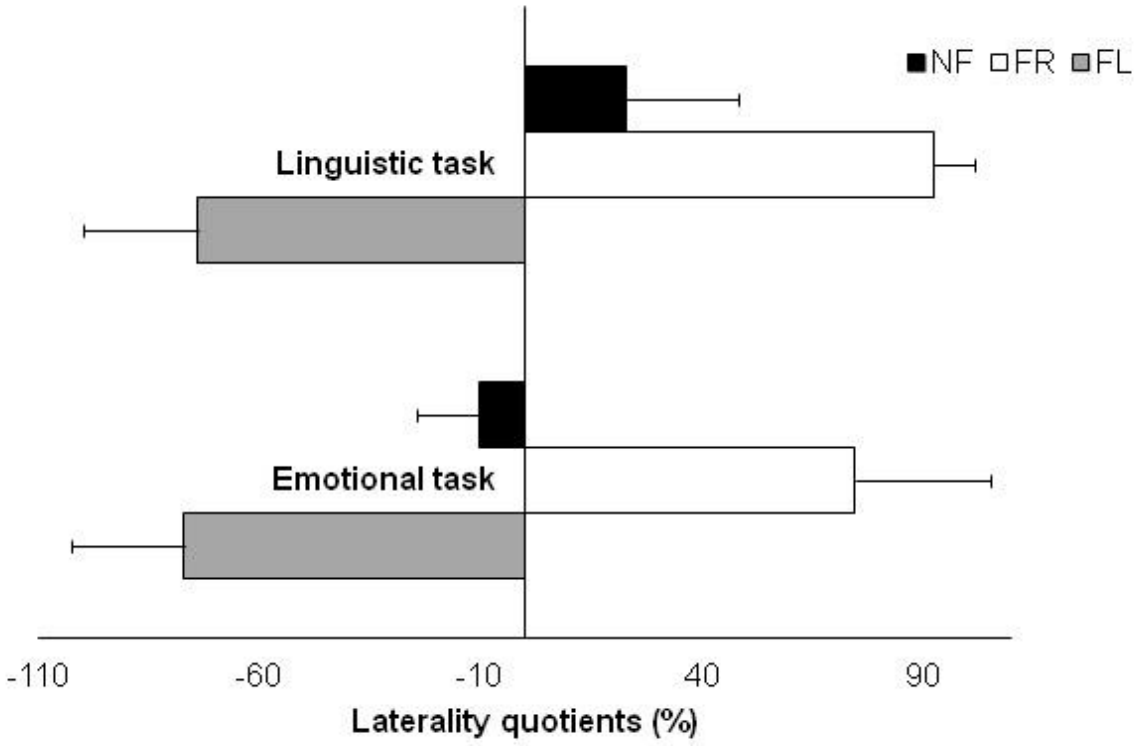

Figure 2. Laterality quotients for each attention condition (non-forced, NF, forced-right FR, forced-left, FL) in both tasks, across all cycle phases. Error bars are standard deviations. One-sample t-tests revealed laterality quotients in both tasks to be significantly different from zero across all conditions (all p < .0001).

Critically, the Task × Condition × Cycle Phase interaction was significant ($F_{(3.38, 82.69)}$ = 2.69, p < .05, η_p^2= .099; see Table 3). The interaction was followed up by two mixed-model

ANOVAs, one for each task with Cycle Phase as the between-subjects factor, and Condition as the within-subjects factor. For the Linguistic task, the Condition × Cycle Phase interaction was not significant ($F_{(4, 98)}$ = 0.34, p = .85, η_p^2 = .01), whereas in the Emotional task, the Condition × Cycle Phase interaction approached significance ($F_{(3.00, 73.58)}$ = 2.13, p = .10, η_p^2 = .08), which appeared to be driven by a reduction in lateralisation in the follicular phase, as compared the menstrual and luteal phases, in the forced-attention conditions of the emotional task only (see Table 3). However, three one-way ANOVAs (one for each attention condition) yielded no significant main effects of Cycle Phase (all F < 2.07, n.s.).

Table 3. Laterality quotients (LQ) and standard deviations for each attention condition of both the emotional and linguistic dichotic listening tasks, according to cycle phase.

	Emotional prosody task			**Linguistic task**		
	Non-Forced M ± SD	**Forced-Right** M ± SD	**Forced-Left** M ± SD	**Non-Forced** M ± SD	**Forced-Right** M ± SD	**Forced-Left** M ± SD
Menstrual	-8.70 ± 13.83	82.44 ± 26.20	-82.63 ± 22.70	26.14 ± 21.56	91.41 ± 9.23	-71.93 ± 23.59
Follicular	-12.06 ± 16.86	63.21 ± 32.98	-68.35 ± 27.63	22.25 ± 28.12	93.78 ± 70.53	-77.72 ± 21.02
Luteal	-10.38 ± 11.30	76.35 ± 30.81	-81.28 ± 24.71	20.66 ± 26.20	92.34 ± 11.05	-71.83 ± 33.30

In order to increase the group difference in estradiol levels (as estradiol levels did not significantly differ between the cycle phases), the data were re-analysed according to an estradiol median split (split score = 3.25 pg/ml) instead of cycle phase, as in the previous study (Hodgetts et al., 2015; Chapter 2). The median split divided the sample into a high and low estradiol group which differed significantly in estradiol levels ($t_{(27.33)}$ = 5.09 p < .001). However, the median split analysis of the dichotic listening data neither revealed a significant main effect of Group ($F_{(1, 50)}$ = .76, p = .76, η_p^2 = .002), nor any interaction with Group approached significance (all F < = 0.47, n.s.).

Similar to Hodgetts et al. (2015), and in order to investigate differences in the degree of lateralisation between the tasks, absolute LQs were also subjected to a 2 × 3 × 3 mixed model ANOVA, with Task (emotional, linguistic) and Condition (non-forced, forced-right, forced-left) as the within-subjects factors, and Cycle Phase (menstrual, follicular, luteal) as the between-subjects factor. The main effect of Task was significant ($F_{(1, 49)} = 13.81$, $p < .001$, $\eta_p^2 = .22$), indicating that the absolute LQ in the linguistic task ($M = 65.02$, $SD = 9.24$) was significantly greater than those in the emotional task ($M = 55.40$, $SD = 16.69$). There was also a main effect of condition, ($F_{(2, 98)} = 314.64$, $p < .001$, $\eta_p^2 = .87$), as the forced attention conditions in both tasks yielded larger absolute LQs compared to the non-forced condition (both $p < .001$). The absolute LQ for the forced-right condition was also larger than that for the forced-left condition ($p < .05$). The Task × Condition interaction was also significant ($F_{(2, 98)} = 7.15$, $p < .001$, $\eta_p^2 = 13$, see Table 4). This interaction reflects the generally larger degree of bias in the linguistic DL task, particularly in the forced-right condition, compared to the emotional prosody task. None of the remaining effects were significant (all $F < 2.51$, n.s.).

Table 4. Absolute laterality quotients (mean ± standard deviation and range) for each attention condition in both tasks, across all cycle phases.

	Non-forced M ± SD (range)	**Forced-right** M ± SD (range)	**Forced-left** M ± SD (range)
Emotional task	14.01 ± 10.35 (0 – 41.67)	74.95 ± 30.40 (0 – 100)	77.24 ± 25.51(0 – 100)
Linguistic task	27.02 ± 20.62 (0 – 76.92)	92.54 ± 9.22 (63.64 – 100)	75.49 ± 20.87 (2.86 – 100)

Relationship between laterality quotients and sex hormones

Since the ANOVA results revealed a significant effect of the Task × Condition × Cycle Phase interaction on dichotic listening biases, we expected estradiol and/or progesterone levels to be significantly related to the laterality quotients in the forced attention conditions of the emotional prosody task. To investigate the relationship between sex hormone levels and dichotic listening biases, we conducted a series of stepwise multiple regression analyses.

Absolute levels of estradiol and progesterone were entered as predictors, and standard laterality quotients from each condition of each task were the dependent variables.

This analysis revealed a significant model for the forced-right condition of the emotional prosody condition only ($F_{(1, 50)}$ = 5.96, p = .01, R^2 = .11). Estradiol was the only significant predictor in this model (β = -.33, p = .01). In line with the ANOVA results, the regression model suggests a negative relationship between estradiol level and lateralisation, specifically in the forced-right (cognitive control) condition of the emotional task. However, the relationship was driven by two participants with considerably high estradiol levels (see Figure 3). Re-running the analysis with these participants excluded resulted in a non-significant model ($F_{(2, 47)}$ = 1.09, p = .35, R^2 = .04).

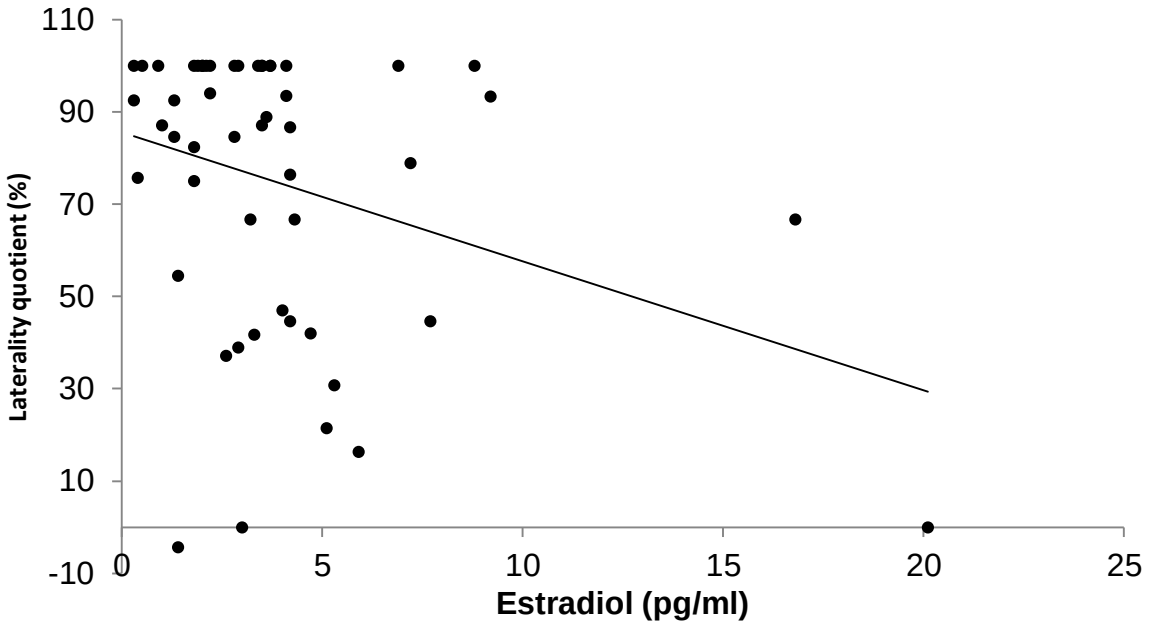

Figure 3. Scatterplot of the relationship between estradiol levels and the laterality quotients of the forced-right condition of the emotional prosody task.

Discussion

The present study demonstrated a significant three-way interaction between task, attention condition, and cycle phase, suggesting that the cycle-related effects on lateralisation

in the forced attention conditions were task-specific. In the emotional prosody based DL task, lateralisation in the forced-right condition was slightly reduced during the follicular phase of the menstrual cycle. Together with the regression analyses, the results suggest that high levels of estradiol, typical of the follicular phase, are related to a reduction in cognitive control, as measured by the forced-attention conditions of the (emotional) DL task. The effects were in contrast to those of Hjelmervik et al. (2012), who reported a significant increase in lateralisation during the forced-left condition of a linguistic DL paradigm in the follicular phase. The authors interpreted this finding as an estradiol-related improvement in cognitive control. However, the apparent reduction in cognitive control in the present study was only small and the significant negative relationship between LQs and estradiol levels in the forced-right condition was driven by a small number of participants with particularly high estradiol levels (Fig 3). Sex hormones did not affect lateralisation in any of the conditions in the linguistic DL task. The findings from the present study were also different to those previously presented by Hodgetts et al. (2015, Chapter 2). In the previous study, a high level of estradiol-reduced language lateralisation, as measured by dichotic listening, was found regardless of attention condition.

Hodgetts et al. (2015), Hjelmervik et al. (2012) and the present study investigated normally cycling women with a linguistic DL paradigm, though stimuli were consonant-vowel syllables in the previous studies, and two-syllable words in the present study. However, while Hodgetts et al. (2015) and Hjelmervik et al. (2012) investigated groups *with* significant differences in estradiol levels, the present study was unable to demonstrate significant, cycle-phase related differences in estradiol. Consequently, previous studies may have been more likely to detect estradiol-related changes in lateralisation. However, the lack of such an effect in the present study is surprising, given that numerically, the mean estradiol levels of the women in the present study were comparable to those reported previously. Moreover, the

median-split analysis, which resulted in groups that *did* differ significantly in estradiol, also did not show hormone-related changes in either language or emotional prosody processing lateralisation. This makes it rather unlikely, that different findings of the present study, compared to previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012) result from differences in estradiol levels between the studies.

One of the main differences between the current and previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012) is the degree of lateralisation. The laterality quotients in the linguistic task of the present study are substantially larger than those seen in previous studies, which used consonant-vowel DL tasks (e.g. Cowell et al., 2011; Hodgetts et al., 2015; Hjelmervik et al., 2012; Wadnerkar et al., 2008) rather than a DL task that required participants to detect a target, as used in the current study. For example, in the non-forced condition of the previous study the mean LQ was 14.71. In contrast, the mean LQs for the linguistic non-forced condition in the present study was 23.01. The difference in the strength of lateralisation generated by the task used in the present study becomes even clearer when the forced attention conditions are considered. For example, in the forced-right condition, the previous sample yielded mean LQs of 44.19. However, in the present study, the mean LQ from the linguistic forced-right condition was 92.54. This is more than double that seen in the previous study, indicating that almost all targets were detected on the forced-attention side in combination with only a very small number of detection errors on the unattended side (the maximum LQ is 100). The large biases demonstrated in the present study are due to the very high target-detection rates observed in almost all participants. Consequently, there is little variation in laterality that remains to be explained by variations in sex hormones. This might also explain some of the inconsistencies in the literature investigating cycle phase-related fluctuations in lateralisation (e.g. Can et al., 2012; Bibawi et al., 1995). For example, Can et al. (2012) also failed to demonstrate sex hormone effects in a DL task (comparable to that used by both Hjelmervik et

al., 2012, and Hodgetts et al., 2015) which revealed considerably larger LQs than those reported previously (average LQ of 47% across cycle phases), despite a larger group difference in estradiol levels than that reported in the current study. In other words, the large DL biases might reflect ceiling effects in target-detection rates that estradiol was unable to further improve.

The generally high target-detection rates and considerably large degree of lateralisation even in the non-forced conditions of the present study, compared to those reported previously, suggests that the task might have been very easy and consequently resulted in very large laterality biases. This stimulus-driven effect might have been so strong that potentially smaller sex hormone-related modulations of cerebral lateralisation were covered. This might be particularly true in the present study, as the cycle-related changes in estradiol levels were only small. The largest detection rates and DL biases were found in the forced-left and forced-right conditions of the linguistic and emotional prosody task, respectively, which were also least sensitive to hormone-related fluctuations. The only condition to show an estradiol-related trend was the cognitive control condition (forced-right) of the emotional task, which also revealed the lowest target detection rates and smallest bias of all forced-attention conditions. These findings suggest that high target-detection rates and large DL biases are less susceptible to sex-hormonal variations. Although the relatively low cognitive demands of the present task resulted in only a small estradiol-related effect, the results also revealed that, in principle, sex hormones are capable of influencing top-down processes in both left (Hjelmervik et al., 2012) and right lateralised tasks (current study).

The suggestion that task-related factors might influence the detection of sex hormonal effects on lateralisation may shed light on some of the inconsistencies in the current literature. A number of studies of language lateralisation have used visual half-field (VHF) tasks, such as word-matching or lexical decision tasks, to investigate sex hormonal effects of lateralisation. Like different DL tasks, different VHF tasks also differ in difficulty and the amount of

cognitive control required. For example word-matching tasks require the participant to decide whether two subsequently presented words are the same, while lexical decision tasks require the participant to discriminate between words and non-words. Although both tasks are performance-based, word-matching tasks are likely more difficult than lexical decision tasks, as participants have to engage working memory processes in order to successfully complete the task. Moreover, in line with the present DL study, the literature suggests that visual half-field studies that are more cognitively demanding (i.e. word-matching tasks) are more likely to demonstrate sex hormonal effects on lateralisation (Chiarello et al., 1989; Weekes & Zaidel, 1996; Weis et al., 2008).

High levels of estradiol were marginally associated with a reduction in lateralisation in the cognitive control condition for the emotional prosody task. This suggests that, unlike the previous study (Hodgetts et al., 2015), the present study is demonstrating a hormonal effect on a specific cognitive (top-down) mechanism, separate to the general (bottom-up) aspect of emotional processing lateralisation. However, this finding should be interpreted with caution because the regression was weak and due to a small number of participants with very high estradiol levels. Also, it should be noted that the regression suggests that high levels estradiol lead to a reduction in cognitive control, which is in direct contrast to Hjelmervik et al. (2012), who demonstrated an estradiol-driven improvement in cognitive control. Critically, the present study showed an estradiol-related reduction in cognitive control specifically in an emotional prosody task. In contrast, Hjelmervik et al. (2012) demonstrated improved cognitive control in a linguistic task only. While this might be due to differences between the tasks used in each study (i.e., target detection as compared to reporting stimuli), an alternative suggestion is that the effect of estradiol on cognitive control is beneficial to linguistic-based tasks, provided they are not strongly lateralised, but detrimental to emotion-based tasks. There is some evidence in the literature that suggests a conflict with some studies reporting estradiol-related

improvements in cognitive control functions (Joffe et al., 2006; Krug et al., 2006; Duff & Hampson, 2000) and others suggesting that estradiol is detrimental to cognitive control (Colzato et al., 2010; Gasbarri et al., 2008; Hatta & Nagaya, 2009). While, these studies do not provide an explanation as to why estradiol might be beneficial to some tasks and not others, the present study suggests that if the tasks employed in these studies vary in their cognitive demands and difficulty, this may explain some inconsistencies in the results.

It is also noteworthy that there is a significant methodological difference between the present study and that presented previously (Hodgetts et al., 2015; Chapter 2). Firstly, while the previous study investigated sex hormone effects using an estradiol-based median split, the present study chose to focus on menstrual cycle phases. Critically, analysing the present data according to an estradiol-based median split resulted in no significant group differences or interactions. However, unlike the previous study, the hormone profiles of participants in the present study appeared to be in concurrence with the participants' self-reported cycle phase. This is likely due to the application of more stringent criteria regarding the cycle days on which participants were tested. For example, in this study, the luteal phase was defined as cycle days 20-22, while the previous study defined this phase as cycle days 15-23. As a result, conducting a median split on the present results in a substantially different hormone profile, as compared to the previous sample. Specifically, across both groups, the present sample yields a higher progesterone level (mean progesterone across both groups = 170.64 pg/ml). Given that progesterone has a predominantly inhibitory effect on neural activity, via GABAergic interactions, it is possible that the higher level of progesterone in the High estradiol group of the present sample was sufficient to counteract any influence of estradiol on cognitive control. This is in line with an earlier notion purported by Smith (1994), who suggested that the excitatory effect of estradiol is dependent on the presence of other steroids in the "background milieu" (p. 67) of hormones

In conclusion, in contrast to previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012; Cowell et al., 2011; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008), the present study did not demonstrate an effect of sex hormones on language lateralisation per se. Instead, the results revealed a significant interaction between sex hormones, task, and attention condition. As such, the present study suggests that tasks with low task demands, resulting in a large degree of lateralisation in the current study, are less sensitive to the effects of sex hormones. This difference in sensitivity might be due to a strong stimulus-driven (bottom-up) effect, resulting in a pronounced difference in activity between the two hemispheres that cannot be modulated by small changes in estradiol. In addition, it should be noted that estradiol levels were only marginally different between the groups in the present study. This might suggest that strongly lateralised tasks require larger group differences in estradiol in order for asymmetries to show cycle-based effects. The lack of a significant difference in estradiol between the groups also highlights the importance of direct, objective hormone measures in menstrual cycle studies. Moreover, for the emotional prosody task, the present study revealed a trend which suggested that estradiol might reduce cognitive control. However, the present study suggested an estradiol-related reduction in cognitive control in an emotional prosody task, as opposed to a linguistic task. This finding suggests that the effect of estradiol on cognitive control may be task-dependent. Consequently, the present study might imply that differences in task type between studies can account for some of the inconsistencies in the literature regarding sex hormonal effects on lateralisation, and cognitive control. This finding is particularly relevant, given the significant amount of inconsistency in the literature sex hormones and lateralisation.

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Chapter 4

Preface

The previous chapters investigated the relationship between sex hormones (particularly, estradiol and progesterone) and cognitive control, in healthy participants. Together, these studies suggest that while estradiol is capable of influencing cognitive control (and lateralisation), it is likely that this effect is dependent upon several factors, such as task type and task difficulty. A separate body of clinical research has shown that estradiol is also capable of influencing the onset, symptoms, and the course of various mental disorders, especially schizophrenia (for a review, see Häfner, 2003).

In general, it has been shown that estradiol may improve psychotic symptoms in women (and men) with schizophrenia (Seeman & Lang, 1990; Häfner, 2003; Riecher-Rössler et al., 1994; Kulkarni et al., 2013). Moreover, schizophrenia is associated with extensive deficits of cognitive control (for a review, see Lesh et al., 2011). Thus, it is possible that the neuroleptic effect of estradiol in psychosis is reflective of its influence on cognitive control abilities. An alternative method by which to investigate the mechanisms of the neuroleptic effect of estradiol is to study non-clinical models of schizophrenia and psychotic symptoms, such as schizotypy. Schizotypy is the term used to describe a multidimensional set of personality traits that represent psychotic-like experiences in the general population (Schofield & Mohr, 2013; Ettinger et al., 2014**).** While such traits are qualitatively similar to the schizophrenic symptomatology, they are quantitatively milder (van Os et al., 2009; Gooding et al., 2006). As such, healthy participants with high levels of schizotypy should demonstrate poor cognitive control, compared to participants with low levels of schizotypy, which is then improved by

estradiol. As such, the following two studies aimed to investigate the effect of estradiol, using non-clinical models of schizophrenia, and psychotic symptoms.[3]

[3] NB: Chapters 2 and 4 present data from the same participants. Chapters 3 and 5 also present data from the same participants. A further exploration of how these studies fit together is presented in the general discussion.

High estradiol levels improve false memory rates and meta-memory in highly schizotypal women

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Abstract

Overconfidence in false memories is often found in patients with schizophrenia and healthy participants with high levels of schizotypy, indicating an impairment of meta-cognition within the memory domain. In general, cognitive control is suggested to be modulated by natural fluctuations in estrogen. However, whether estrogen exerts beneficial effects on meta-memory has not yet been investigated. The present study sought to provide evidence that high levels of schizotypy are associated with increased false memory rates and overconfidence in false memories, and that these processes may be modulated by natural differences in estradiol levels. Using the Deese-Roediger-McDermott paradigm, it was found that highly schizotypal participants with high estradiol produced significantly fewer false memories than those with low estradiol. No such difference was found within the low schizotypy participants. Highly schizotypal participants with high estradiol were also less confident in their false memories than those with low estradiol; low schizotypy participants with high estradiol were more confident. However, these differences only approached significance. These findings suggest that the beneficial effect of estradiol on memory and meta-memory observed in healthy participants is specific to highly schizotypal individuals and might be related to individual differences in baseline dopaminergic activity.

Hodgetts, S, Hausmann, M & Weis, S (2015). High estradiol levels improve false memory rates and meta-memory in highly schizotypal women. *Psychiatry Research,* **229**. 708 - 714

Introduction

Schizophrenia is a severe psychiatric disorder characterised by positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. blunted affect, anhedonia) and cognitive deficits (e.g. cognitive disorganisation). While many aspects of cognition are impaired (Green, 1996; Lesh et al., 2011), it has been purported that memory processes in particular are severely affected (e.g. verbal memory: Toulopoulou and Murray, 2004; working memory: Manoach et al., 2000; see Aleman et al., 1999, for a meta-analysis).

Memory impairments in schizophrenia have been linked to delusions (Moritz and Woodward, 2006), that is, false beliefs characterised by implausibility, which are fixed in spite of evidence to the contrary and asserted with a high degree of confidence (e.g., grandiose delusions, persecutory delusions, paranoid delusions). While delusions are a hallmark of the diagnosis of schizophrenia, an understanding of their neurocognitive basis is still lacking (Gilleen and David, 2005). It has been suggested, though, that delusions are underpinned, at least in part, by a general susceptibility to forming false beliefs/memories with a high level of confidence (Laws and Bhatt, 2005; Moritz and Woodward, 2006). Therefore, investigating the factors influencing confidence in false memories could be of high clinical relevance by improving an understanding of the development and maintenance of delusions, and by potentially influencing individual treatment options for schizophrenia (Favrod et al., 2014; for a review, see Moritz et al., 2014).

To date, false memories in schizophrenia have received comparatively little attention, which might primarily be due to methodological problems. For example, most neurocognitive memory assessments measure recall and recognition accuracy by assessing hit rates, but neglect false recall and recognition, which can be assessed via false positive error rates (Moritz and Woodward, 2006). Those studies that have investigated false memories in schizophrenia have

mainly used the Deese-Roediger-McDermott (DRM) paradigm. In this paradigm, participants study a series of words (e.g. piano, sound, note, sing, melody, band, concert and instrument) that are semantically associated to a non-presented target word (e.g. 'music', the "critical lure", Roediger and McDermott, 1995). Participants are then required to freely recall as many words from the list as possible (recall phase), before being asked to complete a forced choice recognition test on a list comprised of previously seen words. The recognition list is comprised of the critical lure (strongest association to the study list), new words that are related to the study list (strongly associated, but less so than the critical lure), and new words that are unrelated to the study list). Typically, healthy participants falsely remember seeing the critical lure and / or new-related items ("false-positive response"; Roediger et al., 2001), during both the recall and the recognition test. Using this paradigm, it has been shown that while patients have poor recall abilities compared to healthy controls (increased forgetting, Elvevåg et al., 2004), they do not demonstrate increased false recognition (Elvevåg et al., 2004; Moritz et al., 2004). Using the same paradigm, Bhatt et al. (2010) found that patients, both with and without delusions, made more false positive responses during recognition, compared to controls. Moreover, during free recall, patients with delusions produced significantly more false positives than patients without delusions, and healthy controls (see also Brébion et al. 1999; Stirling et al., 1997). Thus, the proneness to false memories seems to be strongly related to the presence of delusions and a possible reason for the inconsistencies in present studies may be that some studies (e.g. Elvevåg et al., 2004; Moritz et al., 2004) did not differentiate between patients with and without delusions.

Considering that generally poorer memory in patients as opposed to healthy controls might confound the formation of false memories (Laws and Bhatt, 2005), an alternative avenue for research employs a non-clinical model of schizophrenia by investigating healthy participants with varying degrees of certain schizotypal personality traits (Ettinger et al., 2014; Johns and

van Os, 2001). Using the DRM paradigm, Laws and Bhatt (2005) investigated false memories in healthy participants, grouped according to their scores on the Peters et al. (2004) Delusional Inventory (PDI); during recall, high PDI scorers produced significantly more false positives compared to low PDI scorers. Saunders et al. (2012) extended these findings to determine which aspects of schizotypy are related to false memories by including a multidimensional schizotypy measure (The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), Mason et al., 2005). The O-LIFE comprises four subscales: Unusual Experiences (i.e. perceptual aberrations and odd beliefs), Cognitive Disorganisation (i.e. attentional difficulties and thought disorganisation), Introvertive Anhedonia (i.e. blunted affect), and Impulsive Non-Conformity (i.e. antisocial behaviour). Saunders et al. (2012) found that high scorers on Unusual Experiences and/or Cognitive Disorganisation produced more false positives during recall compared to low scorers. Consequently, the authors suggest that specific subtypes of schizotypy are more susceptible to false memories, and thus might also be more delusion-prone.

The investigation of memory processes in schizophrenia and schizotypy has recently extended to acknowledge meta-cognitive processes (Bhatt et al., 2010; Moritz et al., 2002; 2003; 2004; 2005; 2006). Meta-memory refers to an individual's knowledge and awareness of their memory capabilities, and the processes of memory self-monitoring (Nelson and Narens, 1990; Pannu and Kaszniak, 2005). While many measures of meta-memory have been developed (Pannu and Kaszniak, 2005), retrospective confidence ratings are most relevant in the context of false memories and delusions. Indeed, Moritz and Woodward (2006) have argued that high confidence in false belief is a "defining feature of delusions" (p.185), and that the level of confidence one has in a (false) memory determines its impact on overt behaviour. That is, one is unlikely to act upon a memory, if one is not confident that it is correct. However, high confidence in a false memory could elicit drastic behavioural consequences.

As a meta-cognitive measure of confidence in false memories, Moritz et al. (2004) introduced the knowledge corruption index (KCI) defined as the proportion of high confidence responses that are errors. Employing the DRM paradigm, these authors found that while patients with schizophrenia and controls did not differ in number of false memories per se, patients made more high confidence errors both when forgetting items that were presented ("misses") and during false positive recognition.

With respect to meta-memory processes in healthy participants with schizotypal traits, Laws and Bhatt (2005) reported higher KCI scores for false memories in high PDI scorers, suggesting they are more confident in their errors than low PDI participants are. Corlett et al. (2009) extended these findings by including multiple schizotypy measures. In line with the findings of Moritz et al. (2004; 2006), highly schizotypal participants did not produce more false positives during recognition than those with low schizotypy. However, a positive correlation was found between schizotypy scores and confidence in false positive responses, particularly for subscales analogous to positive schizophrenic symptoms (e.g. perceptual aberrations, magical ideation). These findings provide further evidence that schizotypy provides an appropriate non-clinical model by which to investigate meta-memory impairments in schizophrenia.

A separate stream of research has shown that estrogen can act as a neuroleptic agent against the symptoms of schizophrenia (Seeman & Lang, 1990; Häfner, 2003; Riecher-Rössler et al., 1994; Kulkarni et al., 2013). Riecher-Rössler et al. (1994) directly investigated the possible neuroleptic properties of estradiol by assessing symptomology across the menstrual cycle. A significant association was found between levels of estradiol and clinical assessment scores; symptoms appeared to improve with increases in estradiol, and deteriorate when estradiol levels decreased. Further research has suggested that memory processes, including working memory (Hampson and Morley, 2013), verbal memory (Joffe et al., 2006), implicit memory (Maki et al., 2002), and discriminability (Keenan et al., 2001) can be enhanced with increased levels of

estrogen (for recent reviews see Duarte-Guterman et al., in press; Frankfurt and Luine, in press). However, it is currently unclear whether the effect of estrogen on memory occurs because of direct effects of estrogen on memory or rather via hormonal effects on memory control functions, such as meta-memory processes (Colzato et al., 2010). Indeed, it has been suggested that the enhancing effect of estrogen is particularly evident during tasks that demand a high level of (meta-) cognitive control, (Hjelmervik et al., 2012; Jacobs and D'Esposito, 2011). Given that meta-memory processes are conceptually comparable to cognitive control processes, it follows that meta-memory abilities should be enhanced under high estrogen conditions.

In summary, previous research has suggested that false memories and impaired meta-memory (indicated by overconfidence in errors) are found both in schizophrenia (potentially providing the basis for the experience of delusions in these patients) and in healthy participants scoring highly on certain schizotypy traits. Still, studies including measures of meta-memory are largely lacking. Another line of research suggests that within memory processes, especially meta-cognitive control functions in memory might be modulated by individual differences in estrogen.

In light of these previous studies, the present study employed a verbal DRM paradigm to further investigate whether or not high levels of schizotypy are characterised by increased false memory rates (indicated by a high rate of false positive responses during recognition) and with impaired meta-memory (as evidenced by high confidence in false memories). In addition, we sought to investigate whether false positive recognition rates and meta-memory abilities are affected by naturally fluctuating estradiol levels.

It was expected that participants with high levels of schizotypy would make more false positive errors than low schizotypy scorers and show overconfidence in these false memories, especially when their estradiol levels were low. Further, it was hypothesised that high levels of

estradiol should have a beneficial effect, especially with respect to meta-cognitive control of false memories.

Method

Participants

Seventy-three healthy, normally cycling women (out of 81 tested; see hormone assessment section for exclusion details) with a mean age of 23 years (S.D. = 4.86; range: 19 – 40 years) were assigned to either the high (n = 37) or low estradiol (n = 36) group, based on saliva estradiol assays (see section 2.2.3 Hormone assays). This method of classification is based on objective quantification of estradiol levels, which are subject to both individual (inter-subject) differences and to natural (intra-subject) fluctuations across the menstrual cycle. Age did not differ significantly between the groups ($t_{(71)} = 1.21$, $p = 0.23$).

All participants were native English speakers with normal or corrected-to-normal vision. Participants did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

Procedure and materials

Schizotypy questionnaire

The short version of the O-LIFE was used to measure schizotypy (Mason et al., 2005). This scale is comprised of four factors: Unusual Experiences, Cognitive Disorganisation, Impulsive Non-conformity, and Introvertive Anhedonia. A schizotypy scale with multiple subscales was applied as the data reported here form part of a larger battery of cognitive tasks (for each of which different subscales might be most relevant). The Cognitive Disorganisation (CD) subscale measures cognitive aspects of schizotypy such as poor attention and concentration (Mason et al., 2005). In light of previous research suggesting that CD is

particularly associated with false memories (e.g. Saunders et al., 2012), this scale is the focus of the current study. Moreover, this scale contains items that directly relate to cognitive control, such as "Are you easily confused if too much happens at the same time?" and "Do you often have difficulties in controlling your own thoughts?". Given that meta-memory processes are essentially cognitive control processes and that estrogen has been shown to have an enhancing effect on cognitive control, this subscale was considered most appropriate, Participants are required to give yes/no responses, and the score is calculated as the sum of all positive answers. A median split was performed based on CD scores (Low CD = 0-4 (M = 2.39 ± 1.29), High CD = 5-11 (M = 7.11 ± 1.75; see Table 1)

Verbal meta-memory task

Six word lists (received and adapted from Moritz et al., (2006) unpublished companion study) comprising 12 semantically associated words each were used for the verbal meta-memory task. The study lists were associated with the following target words: laugh, funeral, road, holiday, time, and panic. The task was completed via a computer using MATLAB (R2013a, MathWorks). For the study phase, participants were presented with the study list, one immediately following another, in the centre of the screen. Each word from the list was presented individually, at a rate of two seconds per word. After all 12 words had been presented; participants were given 75 seconds to freely recall as many words from the list as possible by writing them down (recall phase). The next list was then presented. This procedure was repeated for all six lists. The recognition lists were also made up of 12 words: the critical lure, three new words that are related to the study list ("new-related items"), two new words that are unrelated to the study list ("new-unrelated items"), and six words from the study list ("old items"). For the recognition phase, participants were presented with the recognition list, one word at a time, in a random order, in the centre of the screen. Participants were asked to indicate via button press whether they thought the item was old or new, and how confident they

were in their response on a four-point scale (1-4). Words were not randomised between lists, nor was the order of lists, but the order of words within each list was randomised. There was no time restriction during the recognition phase. The recognition test is the focus of the present paper. From the recognition phase we calculated the number of false positive responses, and knowledge corruption indices ([highly confident false positives /all highly confident responses] × 100)].

Hormone assays

To facilitate collection of a pure saliva sample, women were asked to avoid eating, drinking, smoking and brushing teeth for 30 minutes prior to the testing session. One sample (2 ml) was collected at the beginning of the test session. The saliva was stored -20°C until completion of the study. Samples were then assayed by an independent professional hormone laboratory with commercially available hormone assays. Eight women were excluded from further analyses due to saliva sample contamination by blood, as indicated by sample discolouration and/or extremely high hormone levels out the expected range of the assay. Classification of estradiol as high or low was based on a median-split (split score: 3.4 pg/ml). Mean estradiol and progesterone levels for each group are given in Table 1.

Table 1. Saliva estradiol and progesterone levels and cognitive disorganisation scores for each group (mean±standard deviation).

	Low cognitive disorganisation		**High cognitive disorganisation**	
	Low estradiol N=15	High estradiol N=23	Low estradiol N=21	High estradiol N=14
Estradiol (pg/ml)	2.11±.82	5.37±2.70	2.04 ±.73	6.58±4.53
Progesterone (pg/ml)	77.72±77.19	158.67±111.33	76.91±45.18	130.01±101.03
Cognitive disorganisation	2.27±1.22	2.48±1.34	7.09±1.7	7.14±1.88
Age	22.20±4.39	24.21±6.01	22.38±4.66	22.79±3.40

Results

Salivary hormone concentrations

Estradiol and progesterone levels did not differ between the high CD and low CD subgroups within the low estradiol (LE) (both $t_{(34)} < 0.24$, n.s.) or high estradiol (HE) group (both $t_{(35)} < 1.03$, n.s.)

On the other hand, estradiol levels were significantly higher in the HE than in the LE subgroup, both within the low CD group ($t_{(36)} = 4.52$, $p = < 0.001$) and the high CD group ($t_{(33)} = 4.54$, $p < 0.001$). Similarly, progesterone levels were significantly higher in the HE than in the LE subgroup both within the low CD group ($t_{(36)} = 2.45$, $p = 0.019$) and in the high CD group ($t_{(33)} = 2.12$, $p = 0.041$).

Data analysis

2 × 2 ANCOVAs with estradiol (high, low) and cognitive disorganisation (high, low) as between-subjects factors were conducted on a variety of measures of memory and meta-memory (confidence in memory). Because progesterone has been shown to influence memory process (Ertman et al., 2011), progesterone levels were included as a covariate.

False recognition of critical lure

For the percentage of false-positive responses to the critical lure, the main effects of progesterone, CD group, estradiol group as well as the CD × Estradiol interaction did not reach significance (all $F_{(1, 68)} < 2.09$, $p \geq 0.15$).

Knowledge Corruption Index for false recognition of lure items

The examination of knowledge corruption indices revealed no significant main effects of progesterone, CD group, estradiol group, and the CD × Estradiol interaction did not reach significance (all $F_{(1,68)} < 0.19$, $p \geq 0.66$). Table 2 lists false positive error rates and KCIs for each group.

Table 2. False positive error rates and knowledge corruption indices to critical lure items for each group (means ± standard error).

	Low Cognitive Disorganisation		**High Cognitive Disorganisation**	
	Low estradiol N = 15	High estradiol N = 23	Low estradiol N = 21	High estradiol N = 14
False positives	54.44 ± 7.18	56.52 ± 5.21	57.14 ± 6.56	53.57 ± 4.34
Knowledge corruption index	51.22 ± 8.63	52.61 ± 7.51	58.41 ± 8.65	52.14 ± 9.72

False recognition of new-related items

The ANCOVA on the percentage of false-positive responses revealed a significant interaction between CD group and Estradiol group, ($F_{(1, 68)} = 4.72$, $p = 0.03$, $n_p^2 = 0.07$). Neither the main effects of progesterone, or CD or estradiol group were significant (all $F_{(1, 68)} < 1.28$, $p \geq 0.26$.).

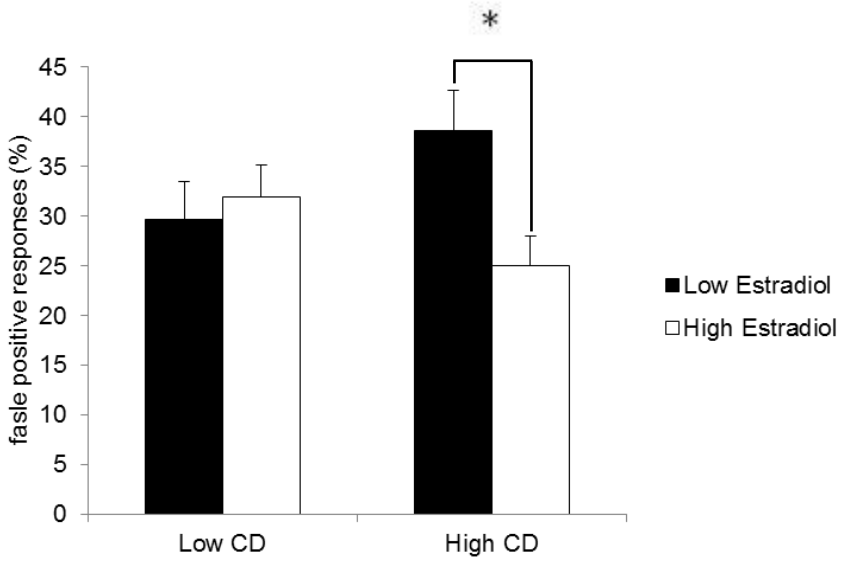

Figure. 1. The interactive effect of estradiol and cognitive disorganisation on false positive response rates for new-related items (error bars are SEMs * = p < 0.05).

Post-hoc t-tests (Bonferroni corrected) revealed that the significant interaction was driven by a significant difference between the HE and LE groups within the High CD group ($t_{(33)} = 2.48$, $p = 0.018$; see Figure 1).

Knowledge Corruption Index for false recognition of new-related items

For the knowledge corruption indices for new-related items a significant interaction between CD group and E group ($F_{(1, 68)} = 5.51$, $p = 0.02$, $n_p^2 = 0.08$) (see Fig. 2) was found. The ANCOVA revealed that the main effects of progesterone, CD, and estradiol group were not significant (all $F_{(1, 68)} < 0.57$, $p \geq 0.45$).

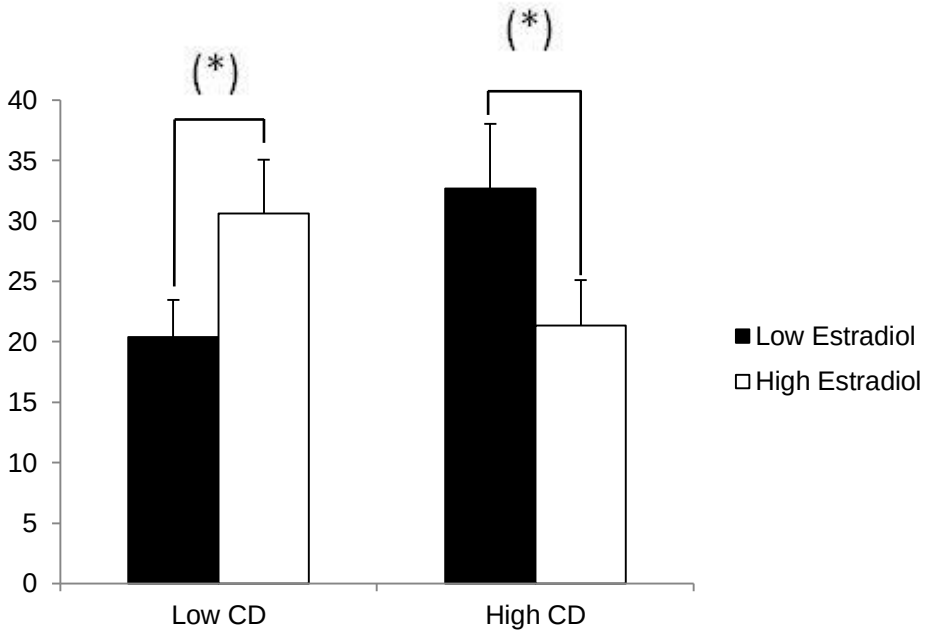

Figure 2. The interactive effect of estradiol and cognitive disorganisation on KCI for new-related items (error bars are SEMs; (*) = $p < 0.15$).

Post-hoc t-tests (Bonferroni) were conducted within each CD group. This revealed that the difference between the HE and LE subgroups approached significance, within both the High CD ($t_{(33)} = 1.57$, $p = 0.13$) and Low CD groups ($t_{(36)} = 1.69$, $p = 0.10$) (see Figure 2). Table 3 lists false positive error rates and KCIs for each group.

Table 3. False positive error rates and knowledge corruption indices to new-related items for each group (means ± standard error).

	Low Cognitive Disorganisation		**High Cognitive Disorganisation**	
	Low estradiol N = 15	High estradiol N = 23	Low estradiol N = 21	High estradiol N = 14
False positives	29.63 ± 3.89	31.88 ± 3.24	38.62 ± 4.01	25.00 ± 2.95
Knowledge corruption index	20.42 ± 3.07	30.64 ± 4.45	32.70 ± 5.32	21.34 ± 3.75

Recognition of old items (misses)

For the percentage of false-negative responses to old items, the main effects of progesterone, CD group, estradiol group as well as the CD × Estradiol interaction did not reach significance (all $F_{(1, 68)} < 1.22$, $p \geq 0.27$).

The examination of knowledge corruption indices also revealed no significant main effects or interactions (all $F_{(1,68)} < 0.013$, $p \geq 0.72$).

Relationship between hormones, schizotypy and meta-memory

The ANCOVA revealed an interactive effect of estradiol and cognitive disorganisation on both false memory rates and knowledge corruption for new-related items. Therefore, we conducted moderated multiple regression analyses (enter method) to investigate any linear relationship between estradiol, progesterone, cognitive disorganisation (and estradiol × CD interaction) and both dependent variables, for the new-related items, in more detail. To avoid multicolinearity, independent (predictor) variables were centered. The CD × E interaction variable was calculated as the product of estradiol and CD (both centered)

For the false memory rate, the moderated multiple regression model was not significant ($F_{(4, 68)} = 0.57$ $p = 0.69$). None of the predictors approached significance (all $\beta < 0.03$, $p \geq 0.28$).

Similarly, the moderated multiple regression model for the KCIs was not significant ($F_{(4, 68)} = 0.46$, $p = 0.77$). None of the predictors approached significance (all $\beta < 0.12$, $p \geq 0.33$).

Discussion

The present study aimed to examine individual differences in false memory rates and meta-memory. It was hypothesised that high levels of cognitive disorganisation would be associated with increased false memory rates and impaired meta-memory, indicated by overconfidence in false memories. Further, the present study sought to investigate whether false memories and meta-memory processes are modulated by differences in estradiol levels, which occur naturally both between and within participants due to fluctuations across the menstrual cycle. We found that participants with high levels of cognitive disorganisation and high estradiol levels produced significantly fewer false memories than highly disorganised participants with low estradiol levels. No effect of estradiol was found in participants with low levels of cognitive disorganisation. Moreover, highly disorganised participants with high levels of estradiol were less confident in their false memories than those with low estradiol. In contrast, participants with low levels of cognitive disorganisation and high estradiol levels were more confident in their false memories than those with low estradiol levels. These findings will be discussed with respect to individual differences in the physiological processes underlying memory and meta-memory, including baseline dopaminergic activity.

Estradiol reduces false recognition in highly schizotypal women.

Investigating false positive rates for experimentally induced false memories revealed an interactive effect of schizotypy and estradiol levels. While increases in estradiol levels did not influence false memory rates in participants scoring low on cognitive disorganisation, high

levels of estradiol were associated with significantly reduced false memory rates in participants high in cognitive disorganisation.

This suggests that estradiol might have a positive effect (reducing false memory rates) specifically in participants with high levels of cognitive disorganisation. While the effect of estradiol on false memories has not yet been directly examined in humans, recent animal studies have demonstrated improved object recognition memory in rats following estradiol treatment (e.g. Frye et al., 2007; Inagaki et al., 2010; Jacome et al., 2010). In contrast to previous studies investigating recognition performance, the present findings suggest that estradiol does not improve false recognition in humans in general. Rather, the effect was specific to participants scoring high on cognitive disorganisation. In addition, no such effects were found for false negative error rates, suggesting that the effects of both estradiol and schizotypy are specific to false memories.

This finding is highly unlikely to be due to higher hormone concentrations in high CD participants, as both CD groups (within the high estradiol group) did not significantly differ in estradiol (or progesterone) levels. Instead, the present findings suggest that the estradiol effect of reducing false memory is specific to individuals with high cognitive disorganisation, and thus those especially prone to false memories.

Estradiol might influence memory via dopaminergic actions

It has recently been suggested that the effect of estrogen on cognition is dependent on individual differences in baseline dopamine function (Colzato and Hommel, 2014). These authors suggest that dopaminergic effects on cognitive tasks (including learning and working memory) follow an ‘Inverted-U’ function; performance improves with medium dopamine levels, but deteriorates with high/low levels. Given that estradiol is associated with higher dopamine turnover rates, Colzato and Hommel (2014) speculate that participants with low

baseline dopamine levels, and thus poor cognitive performance, might benefit from high levels of estradiol and concurrent increases in dopamine. In contrast, estradiol would have detrimental effects in those with high baseline dopamine levels and good cognitive performance, as dopamine increases beyond an optimal point. Indeed, behavioural evidence suggests that schizotypy (and schizotypal personality disorder) is associated with aberrant dopamine function (e.g. Mohr et al., 2004; McClure et al., 2010). Mohr et al. (2004) demonstrated that levodopa (a dopamine agonist) improved visuo-motor performance exclusively in participants with high 'positive' schizotypy (i.e. magical ideation); low schizotypy participants showed a slight performance deterioration with levodopa. Subsequently, Mohr et al. (2004) suggest that high schizotypy is associated with a relative hyperdopaminergia, and a better ability to adapt to higher dopamine levels. If high levels of cognitive disorganisation are associated with relative hyperdopaminergia, this might also explain the improvement in false positive error rates shown by participants high in schizotypy with high estradiol levels, while low schizotypy participants showed a slight (non-significant) impairment.

It is notable that the false memory rates seen in the higher schizotypal participants in the high estradiol group are comparable to those seen in both the low schizotypy subgroups. This might suggest that the effect of estradiol is limited not only to a specific subgroup, but also that it is not enhancing per se, rather estradiol has a 'normalising' effect on false memory rates.

False recognition of the critical lure is not influenced by estradiol or schizotypy

The analysis of responses to the critical lures revealed that neither estradiol nor cognitive disorganisation affected false positive error rates for the lures. This suggests that false memories created by the lure are different to those created by the related items, in that the stronger semantic relationship between the critical lure and the word lists might create a

'stronger' false memory trace. In this case, both schizotypy groups might susceptible to a ceiling effect; that is, the effect of estradiol might not be strong enough to exert a protective effect over false memory rates related to the critical lure. Still, our data suggests that higher levels of estradiol might help improve memory processes in those participants high in CD.

Estradiol reduces false memory confidence in highly schizotypal women

The analysis of confidence in false memories, measured by KCIs, also revealed a significant interaction. In participants scoring high in cognitive disorganisation, high estradiol levels resulted in decreased confidence in false memories, while for participants scoring low on cognitive disorganisation, confidence in false memories was greater with higher estradiol levels. When considering meta-memory as a cognitive control process, the present data suggests that the beneficial effect of estradiol on cognitive control (Hjelmervik et al., 2012; Jacobs and D'Esposito, 2011; Keenan et al., 2001) might be specific to participants with high cognitive disorganisation, at least within the domain of memory.

Recent evidence suggests that meta-cognitive processes, like memory processes, can be influenced by dopamine. Using magnetoencephalography during a forced-choice word recognition paradigm, Joensson et al. (2015) demonstrated improved meta-cognitive ability in participants who received 100mg of L-dopa, as compared to placebo. In addition, dopamine administration was associated with increased activity of the medial prefrontal cortex.

It is notable that a similar interaction was found for both memory performance, measured by the rate of false positives, and meta-memory as measured by KCI. For both measures, participants scoring high in cognitive disorganisation benefitted from high levels of estradiol. However, this improvement was significant for the false positive error rates only, suggesting that the objective measures (false positive error rates) might be more sensitive to the effects of schizotypal traits and estradiol levels. This finding supports the notion that the

inclusion of both objective (e.g. false positive error rates) and subjective measures (e.g. memory confidence) is important when investigating memory process across the schizophrenic spectrum.

The relationship between sex hormones, schizotypy and memory processes

The present study failed to demonstrate a linear relationship between the interactive effect of estradiol and schizotypy on either false positive error rates or knowledge corruption. However, it is possible that the relationship between these factors it is not linear. Indeed, findings from a recent animal study suggest that the enhancing effects of estradiol on recognition abilities are non-linear. Inagaki et al. (2010) demonstrated that medium doses of estradiol (17α-estradiol) were most effective, while high and low doses were ineffective. An alternative explanation for the lack of a significant relationship is that the observed estrogenic effects are not directly related to estradiol but another estrogen, such as estrone. Indeed, Louzā et al. (2004) reported that schizophrenic patients given an adjunctive estrone treatment showed a trend towards greater symptom improvement than patients given an adjunctive placebo. The authors note, however, that this effect was not comparable to the significant improvements seen in patients with 17β-estradiol (e.g. Kulkarni et al., 1996; 2001). Moreover, given that estradiol is the most potent agonist of estrogen receptors (Turgeon et al., 2004), it seems unlikely that estrone is related to the current findings.

Importantly though, the present results may explain some of the inconsistent findings with respect to false memories in schizophrenia, which typically do not control for differences in the hormonal environment (e.g. menstrual cycle). Specifically, if estradiol levels are high in patients the risk of false memories might be reduced, as suggested by the high CD group of the present study. Thus, differences between patients and controls may only be apparent when estradiol levels are low in female patients, or when males dominate patient samples. For

example, Bhatt et al. (2010) demonstrated elevated false positive recognition in both delusional and non-delusional schizophrenic patients compared to controls. In this study, both patient groups were male-dominated (12 men 1 woman, and 11 men, 1 woman respectively). Similarly, using a stem completion task, Stirling et al. (1997) report increased rates of false recall in patients compared to controls. This patient sample contained 22 males to 5 females. However, using a gender-balanced patient sample (18 males, 17 females) Moritz et al. (2006) found no excess of false positive error rates in patients. Although these studies also vary in task type, these results suggest that, in conjunction with the present study; differing hormonal environments between participants may modulate differences between patients and controls (but see Moritz et al., 2004).

Conclusions

In conclusion, the present study demonstrated that high levels of estradiol resulted in reduced rates of false memories together with a reduction of an over-confidence in these memories in participants with high levels of schizotypy, specifically cognitive disorganisation. Considering that overconfidence in false memories is key to the development and maintenance of delusional symptoms, these results provide additional support for the potential role of estrogen as a neuroprotective agent against the symptoms of schizophrenia (Seeman and Lang, 1990; Riecher-Rössler et al., 1994; Kulkarni et al., 1996). Moreover, these findings lend further support to the notion that estradiol effects are dependent upon individual differences in the neurophysiology underlying cognitive processes (e.g. baseline dopamine function). For example, a relative hyperdopaminergia (at baseline) in participants with high levels of cognitive disorganisation might explain the improvement in false positive error rates shown by these participants with high estradiol levels, while low schizotypy participants demonstrated a slight impairment. Finally, in the clinical context, the present results underline the importance

of taking individual differences into account when devising tailored treatment options for schizophrenia.

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Chapter 5

Estradiol does not improve false memory rates and meta-memory for emotional stimuli in highly schizotypal women

Abstract

Patients with schizophrenia and healthy participants with high levels of schizotypy tend to demonstrate overconfidence in false memories, indicating impairments in cognitive control of memory function. Additional studies have shown that cognitive control can be modulated by natural fluctuations in estrogen. A recent study (Hodgetts et al., 2015) demonstrated that estradiol may have a beneficial effect on memory and meta-memory, but only in participants with a high level of cognitive disorganisation. As emotion has been shown to increase false memory rates in healthy participants, we sought to investigate whether schizotypy would support or suppress this effect. We also aimed to investigate whether estradiol would provide a protective effect against false memories and false memory confidence, despite the enhancing effect of emotion. Fifty-two natural cycling women completed a verbal Deese-Roediger-McDermott paradigm involving emotionally salient word lists. The results showed that highly schizotypal participants with high estradiol levels did not produce a lower number of false memories, or a lower level of confidence compared to those with a lower estradiol level. However, a consistent effect of emotion was found, with negative stimuli producing a greater number of false memories, and a higher degree of confidence. In addition, an interaction between emotion, schizotypy and estradiol was found for both the false memory rates and meta-memory. These findings suggest that the beneficial effect of estradiol on memory and meta-memory observed in highly schizotypal participants does not occur for emotionally salient stimuli.

Introduction

Schizophrenia is a severe psychiatric disorder characterised by psychosis (hallucinations, delusions) and cognitive deficits (e.g. cognitive disorganisation). While many aspects of cognition are impaired (Green, 1996; Lesh et al., 2011), it has been purported that memory processes are particularly affected (e.g. verbal memory: Toulopoulou and Murray, 2004; working memory: Manoach et al., 2000; see Aleman et al., 1999, for a meta-analysis). Memory impairments in schizophrenia have been linked to delusional symptoms (Moritz and Woodward, 2006). Delusions manifest as false beliefs characterised by implausibility, which are fixed in spite of evidence to the contrary and asserted with a high degree of confidence (e.g., grandiose delusions, persecutory delusions, paranoid delusions). It has been suggested that delusions are underpinned, at least in part, by a general susceptibility to forming false beliefs/memories with a high level of confidence (Laws and Bhatt, 2005; Moritz and Woodward, 2006).

Studies that have investigated false memories have mainly used the Deese-Roediger-McDermott (DRM) paradigm. In this paradigm, participants study a series of words (e.g. piano, sound, note, sing, melody, band, concert and instrument) that are semantically associated to a non-presented target word (e.g. 'music', the "critical lure", Roediger and McDermott, 1995). Participants are then required to freely recall as many words from the list as possible (recall phase), before being asked to complete a forced choice recognition test on a list of previously seen and new words. The new words typically comprise the critical lure (strongest association to the study list), new words that are related to the study list (strongly associated, but less so than the critical lure), and new words that are unrelated to the study list. It been consistently shown that healthy participants tend to falsely remember seeing the critical lure and / or new-related items ("false-positive response"; Roediger et al., 2001), during both the recall phase and the recognition test, while the results of such studies in patients with schizophrenia have

been inconsistent. Indeed, some studies report an increased rate of false memories in patients (Bhatt et al., 2010; Brébion et al., 1999; Stirling et al., 1997) while others find no difference between patients and controls (Elvevåg et al., 2004; Moritz et al., 2004). Still further studies have investigated false memory formation in healthy participants with non-clinical schizotypal personality traits. For example, Laws and Bhatt (2005) investigated false memories in healthy participants, grouped according to their scores on the Peters et al. (2004) Delusional Inventory (PDI); during recall, high PDI scorers produced significantly more false memories compared to low PDI scorers. Moreover, Saunders et al. (2012) found that healthy participants with a high level of cognitive disorganisation (i.e. attentional difficulties and thought disorganisation) produced more false memories during recall compared to low scorers.

The investigation of memory processes across the schizophrenia spectrum has recently extended to acknowledge meta-memory processes (Bhatt et al., 2010; Hodgetts et al., 2015; Moritz et al., 2002; 2003; 2004; 2005; 2006). Meta-memory refers to an individual's knowledge and awareness of their memory capabilities (Nelson and Narens, 1990; Pannu and Kaszniak, 2005) such as memory confidence. Indeed, Moritz and Woodward (2006) have argued that high confidence in a false belief is a "defining feature of delusions" (p.185). To investigate false memory confidence Moritz et al. (2004) introduced the knowledge corruption index (KCI) to the DRM paradigm, in addition to the error rates acquired from the recall and/or recognition phases. The KCI is defined as the proportion of high confidence responses that are errors. These authors found that patients with schizophrenia were more confident in their 'miss' responses (i.e. forgotten items) and in their false positive responses (i.e. false memories), compared to controls. With respect to schizotypy, Laws and Bhatt (2005) reported higher KCI scores for false memories in high PDI scorers, suggesting they are more confident in their errors than low PDI participants are. Corlett et al. (2009) extended these findings by including multiple schizotypy measures. In this study, a positive correlation was found between confidence in false

positive responses and particularly those schizotypy subscales analogous to positive psychotic symptoms (e.g. perceptual aberrations, magical ideation). Furthermore, these findings support the notion that schizotypy is an appropriate, non-clinical model by which to investigate meta-memory impairments in schizophrenia.

Emotional content has consistently been shown to influence memory, for both healthy participants, and patients with schizophrenia. In healthy participants, emotional content typically elicits a higher degree of accurate recall and recognition compared to neutral stimuli (e.g. Bradley et al., 1992; Kensinger & Corkin, 2003; Hamann et al., 1999; see Kensinger. 2004 for a review). In contrast, patients with schizophrenia often exhibit poor recall and/or recognition for emotionally salient stimuli. For example, Herbener et al. (2007) demonstrated decreased recall for positive material in patients with schizophrenia while Hall et al. (2007) reported decreased recall of both positive and negative material in patients. However, in contrast, Danion et al. (2003) reported better recognition of emotional stimuli compared to neutral stimuli in patients, in spite of generally poor recognition performance. Moreover, Neumann et al. (2007) demonstrated that emotional stimuli affected patients and controls differently, with patients exhibiting poor recognition of negative compared to positive stimuli, and controls showing the opposite pattern.

Additional studies have investigated emotionality effects on false memory and meta-memory in healthy participants. With respect to false memories, such studies have shown that emotionality can either increase or decrease false memory rates (Choi et al., 2013). For example, Pesta et al. (2001) demonstrated that participants falsely remembered neutral lures more often than they did emotional lures, while El Sharkawy et al. (2008) reported that negative word lists were associated with more false memories than neutral lists. While studies of emotion effects on meta-memory in healthy participants are somewhat limited, a recent review (Fairfield et al., 2015) concluded that the effect of emotion of meta-memory is variable according to valance

(positive or negative). Moreover, different aspects of meta-memory (e.g. judgments of learning, feeling of knowing) appear to be differently affected by emotional stimuli (Fairfield et al., 2015). For example, in judgment of learning tasks, participants are asked to state how confident they are that they will remember a studied item during a later memory test. Using this task, Zimmerman and Kelley (2010) showed that judgments of learning for emotional stimuli were no more accurate than those for neutral stimuli. In contrast, Thomas et al. (2011) used a feeling of knowing task, in which participants were asked to predict how likely they were to recognise an item they previously failed to recall. In this study, participants were given a cued recall test, and asked to provide a feeling-of-knowing judgment if they could not produce the target item. After providing the judgment, they were asked to rate the emotional valence of the target as either "good" or "bad". Results showed that the accuracy of participants' feeling of knowing judgments was not dependent on emotional valance per se, but on the accuracy of their recall of contextual information. For example, participants produced more accurate judgments when they correctly recalled a target as either "good" or "bad".

Studies of emotional effects on meta-memory in schizophrenia and schizotypy are also limited, and have provided equivocal results (Moritz et al., 2006; Peters et al., 2013; Kaney et al., 1992). Moritz et al. (2006) used a visual variant of the DRM paradigm in order to investigate the effect of emotional content on false memory confidence in patients with schizophrenia. In this study, patients were presented with a series of images with specific emotional themes (e.g. a positive image (beach), a negative image (funeral), a neutral image (classroom), and a "paranoid delusion" image (room surveillance)). The authors hypothesised that patients would produces a higher rate of false memories for mood congruent stimuli. However, the results showed that patients and controls did not differ in their rate of false memories, or their confidence (but see Kaney et al., 1992). Peters et al. (2013) also adopted a visual variant of the DRM paradigm, using a series of emotional videos to elicit false memories (e.g. positive video

(children's birthday party), negative videos (a fight scene, and footage from a car accident), a neutral scene (electrician at work), and a delusion-based scene (police surveillance)). Patients and controls showed a similar number of false memories for all videos, with the exception of the positive video. For this video, patients had a higher number of false memories compared to controls. Moreover, patients also showed an overconfidence in false memories, as compared to controls, but this was not affected by the emotional content of the videos. With respect to schizotypy, Hoshi et al. (2011) demonstrated that recall of a verbal narrative was not affected by emotional content in highly schizotypal participants. In contrast, all participants showed the expected emotion-related enhancement for recognition memory. To date, the effect of emotion on false memories and meta-memory processes (such as overconfidence), has not yet been investigated in schizotypal participants.

An independent line of research has shown that estrogen, and specifically estradiol, can act as a neuroleptic agent against the symptoms of schizophrenia (Seeman & Lang, 1990; Hafner, 2003; Riecher-Rössler et al., 1994; Kulkarni et al., 2013). Still further research has suggested that memory processes, including working memory (Hampson and Morley, 2013), verbal memory (Joffe et al., 2006), implicit memory (Maki et al., 2002), and discriminability (Keenan et al., 2001) can be enhanced with increased levels of estrogen (for recent reviews see Duarte-Guterman et al., 2015; Frankfurt & Luine, 2015). However, it has been suggested that the effect of estrogen on memory occurs not because of direct effects of estrogen on memory, but rather via hormonal effects on memory control functions, such as meta-memory processes (Colzato et al., 2010). Indeed, it has been suggested that the enhancing effect of estrogen on cognition in general is particularly evident during tasks that require a high level of (meta-) cognitive control (Hjelmervik et al., 2012; Jacobs and D'Esposito, 2011). Given that meta-memory processes are conceptually comparable to cognitive control processes, it follows that meta-memory abilities should be enhanced under high estrogen conditions.

Taken together, previous research has suggested that false memories and impaired meta-memory (indicated by overconfidence in errors) are found both in patients with schizophrenia and in healthy participants with high levels of schizotypal personality traits. Another line of research suggests that within memory processes, especially meta-cognitive control functions in memory might be modulated by individual differences in estrogen. In light of these previous studies, a recent study (Hodgetts et al., 2015; Chapter 4) aimed to investigate whether false positive recognition rates and overconfidence in errors in schizotypal participants would be affected by naturally occurring inter-individual differences in estradiol levels. Using a verbal DRM paradigm, it was found that highly schizotypal participants (those with a high level of cognitive disorganisation) with high estradiol levels produced significantly fewer false memories than those with low estradiol levels. Highly schizotypal participants with high estradiol levels were also less confident in their false memories, compared to those with low estradiol. Given that estradiol did not affect the number of false memories in participants with a low level of schizotypy, and appeared to increase overconfidence in errors in these participants, it was concluded that estradiol may have a beneficial effect on memory and meta-memory, but only in participants with a high level of cognitive disorganisation.

The present study aims to extend the findings of Hodgetts et al. (2015) by introducing emotionality as an additional factor that might interact with estradiol to influence false memory rates, and meta-memory. Like the previous study, a verbal DRM paradigm was used. However, in contrast to the previous study, the word lists used here were designed to be emotionally salient (positive, negative, and neutral). The neutral condition was included with the aim of replicating the previous finding, of an estradiol-driven improvement in false memory rates and meta-memory, in high schizotypal women. Given that emotional material (particularly negative stimuli) is more salient, leading to more memories (and more false memories), we expected a higher rate of false memories for the negative word lists relative to the positive and neutral

ones. We sought to investigate whether this effect is supported or suppressed by schizotypal traits. Moreover, given that estradiol was previously shown to influence memory and meta-memory in highly schizotypal participants, we sought to investigate whether estradiol would still protect against false memories (and false memory confidence), despite them being more pronounced on account of the enhancing effects of emotion.

Method

Participants

Fifty-two healthy, normally cycling women (out of 55 tested; see Hormone Assessment section for exclusion details) with a mean age of 25.15 years (S.D. = 6.60 range: 19-41 years) were assigned to either the high (n = 26) or low estradiol (n = 26) group, based on saliva estradiol assays. This method of classification is based on objective quantification of estradiol levels, which are subject to both individual (inter-subject) differences and to natural (intra-subject) fluctuations across the menstrual cycle. Age did not differ between the groups ($t_{(50)}$ = 0.38, p = .71).

All participants reported no current/previous psychiatric or neurological illness, and had normal/corrected-to-normal vision. Participants were not pregnant and did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

Procedure and materials

Pilot study

Stimuli for this task were developed and piloted by the authors. A list of 81 words (27 positive, 27 negative and 27 neutral) were taken from Bradley and Lang's (1999) Affective Norms for English Words. Positive words were selected on the basis that they had a mean valence score of eight or more, neutral words scored between five and six, and negative words

scored two or less. This list of words was piloted on a sample of 20 female, native English speakers. Participants were asked to rate the emotionality of each word on a scale from minus five (most negative) to plus five (most positive), with zero being neutral. A mean score was computed for each word. The three most negative, most positive and most neutral were then selected as the lure words, resulting in nine word lists. For each lure word, a corresponding list of 15 strongly associated words, was developed using the Nelson, McEvoy and Schreiber's (1998) list of 'Free Association Norms' (a database that provides lists of normed associations for target words), 12 of the associated words were used to the form the study list. Each of the nine recognition lists comprised six, randomly chosen words from the studied list ("old" items), the remaining three unstudied words ("new-related" items), two unrelated words, and the lure word.

Emotional verbal meta-memory task

The study lists were associated with the following "lure" items: arm, foot, engine (neutral), danger, death, murder (negative), friend, fun, wedding (positive). The task was completed via a computer using Psychtoolbox in MATLAB (R2013a, MathWorks). For the study phase, participants were presented with the study lists, one immediately following another. Each word from the list was presented individually in the centre of the screen at a rate of two seconds per word. Participants were then given 75 seconds to freely recall as many words as possible for the list by writing them down (recall phase). The next list was then presented. This procedure was repeated for all nine lists. For the recognition phase, participants were presented with the recognition list, one word at a time, in the centre of the screen. Participants were asked to indicate via button press whether they thought the item was old or new, and how confident they were in their response on a four-point scale (1-4). The order of the lists and the order of words within each list were randomised between participants. There was no time restriction during the recognition phase. The recognition phase is the focus of the

present chapter. For this phase, we calculated the number of false positive responses, and knowledge corruption indices. The knowledge corruption index was calculated using only responses given a "confident" rating (i.e. "old and confident" or "new and confident") using the following formula: [(high confident false positives/all highly confident responses) × 100].

Hormone assessment

Two saliva samples were collected during each session, one before the memory task, and one after (2 × 1ml). To facilitate the collection of the samples, all participants were asked to avoid eating, drinking, smoking, chewing gum or brushing their teeth for 30 minutes prior to the test session. The saliva was stored at -20°C until completion of the study. Samples were assayed by an independent, professional hormone laboratory with commercially available luminescence immunoassays for estradiol and progesterone. The analysis was completed on an average amount of the two samples. The sensitivity of the estradiol assay was 0.3 pg/ml, the sensitivity of the progesterone was 2.6 pg/ml. Intra-assay coefficients for estradiol and progesterone were 13.3% and 6%, respectively.

Three women were excluded from further analyses due to progesterone levels exceeding the range of the assay (<1000 pg/ml) or contamination by blood. Mean estradiol and progesterone levels for each group are given in Table 1.

Schizotypy questionnaire

The short version of the O–LIFE was used to measure schizotypy (Mason et al., 2005). This scale is comprised of four factors: Unusual Experiences, Cognitive Disorganisation, Impulsive Non-conformity, and Introvertive Anhedonia. A schizotypy scale with multiple subscales was applied as the data reported here form part of a larger battery of cognitive tasks (for each of which different subscales might be most relevant). The Cognitive Disorganisation (CD) subscale measures cognitive aspects of schizotypy such as poor attention and

concentration (Mason et al., 2005). In light of previous research suggesting that CD is particularly associated with false memories (e.g. Saunders et al., 2012), this scale is the focus of the current study. Moreover, this scale contains items that directly relate to cognitive control, such as "Are you easily confused if too much happens at the same time?" and "Do you often have difficulties in controlling your own thoughts?". Given that meta-memory processes are essentially cognitive control processes and that estrogen has been shown to have an enhancing effect on cognitive control, this subscale was considered most appropriate, Participants are required to give yes/no responses, and the score is calculated as the sum of all positive answers. A median split was performed based on CD scores (Low CD = 0–4 (M = 2.13 ± 1.60), High CD = 5–10 (M = 6.59 ± 1.59; see Table 1).

Table 1. Estradiol, progesterone, cognitive disorganisation and age (mean ± standard deviation and range) for all women in each group.

	Low cognitive disorganisation		**High cognitive disorganisation**	
	Low Estradiol (n = 12)	**High Estradiol (n = 11)**	**Low Estradiol (n = 14)**	**High Estradiol (n = 15)**
Estradiol (pg/ml)	1.93 ± 0.92 (0.3 – 3.0)	5.49 ± 3.86 (3.40 – 16.80)	1.69 ± 0.86 (0.30 – 0.86)	6.31 ± 4.32 (3.30 – 20.10)
Progesterone (pg/ml)	157.75 ± 99.37 (46.00 – 387.00)	190.72 ± 117.60 (52.00 – 419.00)	107.93 ± 45.43 (68.00 – 205.00)	224.73 ± 125.45 (68.00 – 510.00)
Cognitive disorganisation	2.58 ± 1.56 (0 – 4)	1.64 ± 1.57 (0 – 4)	6.64 ± 1.45 (5 – 10)	6.53 ± 1.77 (5 – 10)
Age	27.58 ± 7.36 (20 – 41)	27.36 ± 8.05 (19- 41)	23.71 ± 5.34 (19 – 35)	22.93 ± 5.22 (19 – 38)

Results

Salivary hormone concentrations

Estradiol and progesterone levels were subjected to a 2 × 2 ANOVA, with estradiol group (high, low) and cognitive disorganisation (high, low) as between-subjects factors.

For estradiol, only the main effect of estradiol group was significant ($F_{(1, 48)} = 23.94$, $p < .001$, $\eta_p^2 = .33$), with significantly higher estradiol levels in the HE group compared to the LE group. There was no main effect of CD group, and no interaction between CD and estradiol group (both $F < .41$, n.s.).

Similarly for progesterone, only the main effect of estradiol group was significant ($F_{(1, 48)} = 6.98$, $p < .05$, $\eta_p^2 = .13$), with significantly higher progesterone levels in the HE group compared to the LE group. There was no main effect of CD group, and no interaction between CD and estradiol group (both $F < 2.19$, n.s.).

Data analysis

3 × 2 × 2 mixed-model ANOVAs, with emotion (positive, negative, neutral) as the within-subjects factor, and cognitive disorganisation (high, low) and estradiol (high, low) as the between-subjects factors were conducted on measures of memory (false positives) and meta-memory (knowledge corruption).

False recognition of critical lure

For the percentage of false-positive responses to the critical lure, only the main effect of Emotion reached significance ($F_{(2, 96)} = 16.24$, $p < .001$, $\eta_p^2 = .25$). Pairwise comparisons (Bonferroni) showed that there were significantly fewer false positive responses to both the neutral and positive lists compared to the negative list (both $p < .001$). There was no significant

difference between the neutral and positive lists (p = .29). None of the interaction effects or between-subjects effects were significant (all F < 1.15, p > .32).

Knowledge corruption index for false recognition of lure items

For the knowledge corruption index for lure items, there was a significant main effect of Emotion ($F_{(2, 96)}$ = 16.27, p < .001. η_p^2 = .25). Similar to the previous analysis, pairwise comparisons (Bonferroni) revealed significantly higher confidence in errors for the negative lists, as compared to both the neutral and positive lists (both p < .001). There was no significant difference in KCIs between the neutral and positive lists (p = .28). In addition, the Emotion × Estradiol group interaction also reached significance ($F_{(2, 96)}$ = 3.19, p = .046, η_p^2 = .062) (see Figure 1.).

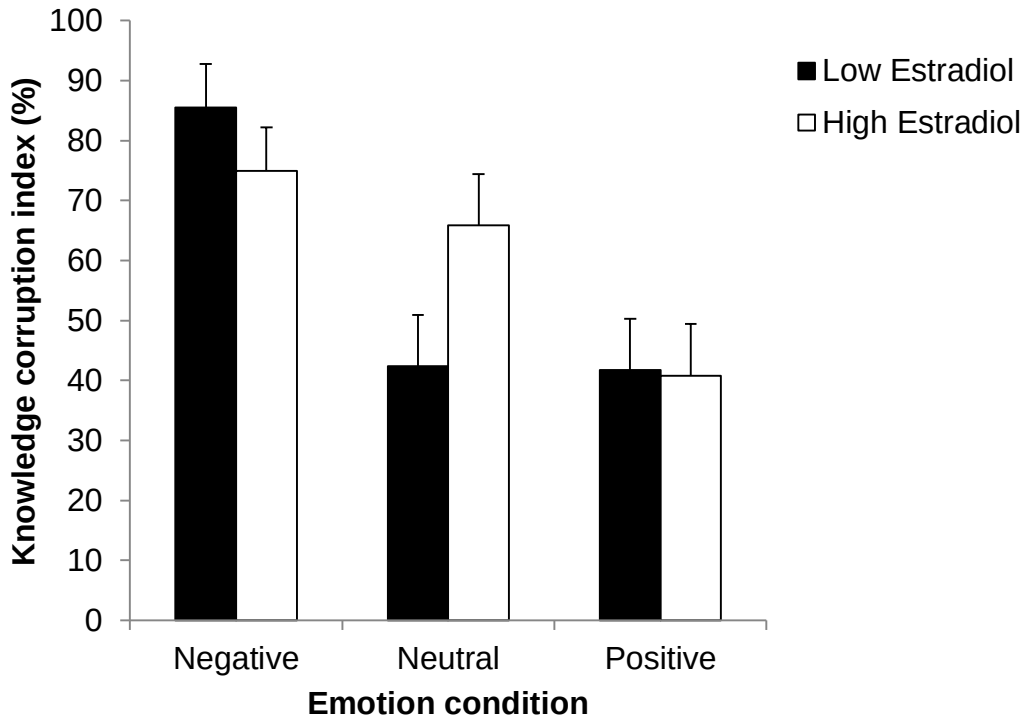

Figure 1. The interactive effect of estradiol and emotion on knowledge corruption indices for lure items. Error bars are SEMs.

To follow up the interaction, two repeated measures ANOVAs were conducted, with Emotion as a within-subjects factor, for each Estradiol group. A significant effect of Emotion was found for both the Low estradiol ($F_{(2, 50)} = 13.86$, $p < .001$, $\eta_p^2 = .36$) and the High estradiol group ($F_{(2, 50)} = 6.54$, $p < .005$, $\eta_p^2 = .21$). For the Low estradiol group, post-hoc pairwise comparisons (Bonferroni) revealed significantly higher KCIs for the negative list compared to both the neutral and the positive lists (both $p < .001$). In contrast, for the High estradiol group, the only significant difference was between the negative and positive conditions ($p = .003$), with the negative condition yielding higher KCIs than the positive condition. In addition, the neutral condition yielded higher KCIs than the positive condition, although this difference only approached significance ($p = .07$). A series of additional post-hoc t-tests (Bonferroni) between the estradiol groups for each emotion condition yielded no significant differences (all $t > 1.45$, n.s.). None of the remaining interactions, or the between-subjects reached significance (all $F < 1.17$, $p > .29$). Table 2 lists false positive error rates and KCIs for each group.

Table 2. False positive error rates and knowledge corruption indices to lure items for each emotion, for each group (means ± standard deviation).

	Low cognitive disorganisation		**High cognitive disorganisation**	
	Low estradiol (N = 12)	**High estradiol** (N = 11)	**Low estradiol** (N = 14)	**High estradiol** (N = 15)
False positives				
Negative	83.34 ± 22.47	78.79 ± 34.23	78.57 ± 24.83	75.56 ± 29.46
Neutral	55.56 ± 29.59	60.61 ± 35.96	52.38 ± 28.39	62.22 ± 37.51
Positive	44.44 ± 35.77	48.48 ± 37.61	38.33 ± 31.34	59.99 ± 36.08
Knowledge corruption				
Negative	88.89 ± 29.59	74.24 ± 40.39	82.14 ± 37.25	75.56 ± 38.25
Neutral	51.38 ± 43.49	72.72 ± 41.01	33.33 ± 42.87	58.89 ± 45.80
Positive	51.39 ± 45.76	39.39 ± 43.64	32.14 ± 42.59	42.22 ± 41.72

False recognition of new-related items

As in the previous analyses, the ANOVA for the percentage of false-positive responses to new-related items revealed a significant main effect of Emotion ($F_{(2, 96)} = 41.53$, $p < .001$, $\eta_p^2 = .46$). Pairwise comparisons revealed that there was a significantly higher number of false-positives for the negative list, as compared to both the neutral and positive lists (both $p < .001$). Moreover, there were significantly fewer false-positives for the neutral list, as compared to the positive list ($p < .05$). More importantly, the analysis revealed a significant interaction between CD group, Estradiol group, and Emotion ($F_{(2, 96)} = 3.41$, $p = .04$, $\eta_p^2 = .07$).

The interaction was followed up with two 3 × 2 mixed model ANOVAs, with Emotion as the within-subjects factor and Cognitive disorganisation as the between subjects factor, for each Estradiol group. For the Low estradiol group, the ANOVA revealed a significant main

effect of Emotion ($F_{(2\ ,\ 48)}$ = 17.52, p < .001, η_p^2 = .42), driven by a significantly higher rate of false positives in the negative condition compared to the neutral and positive conditions (both p < .01). The Emotion x CD interaction did not approach significance ($F_{(2,\ 48)}$ = 1.33, p = .275, η_p^2 = .05). The between subjects effect of CD group also did not approach significance ($F_{(1,\ 24)}$ = 1.21, p = .283, η_p^2 = .048). Similarly, for the High estradiol group, the ANOVA revealed a significant main effect of Emotion ($F_{(2,\ 48)}$ = 25.57, p < .001, η_p^2 = .52). As before, this was driven by a significantly higher error rate in the negative condition compared to both the negative and the neutral conditions (both p > .001). In addition, the neutral condition yielded significantly lower error rates compared to the positive condition (p = .049). There was no between subjects effect of CD group (p = .987). In contrast to the same analysis in the Low estradiol group, the Emotion × CD interaction approached significance in the High estradiol group ($F_{(2,\ 48)}$ = 2.54, p = .089, η_p^2 = .096; see Figure 2). However, a series of post-hoc t-tests (Bonferroni corrected) to compare the High and Low CD groups at each emotion condition yielded no significant differences (all p > .21).

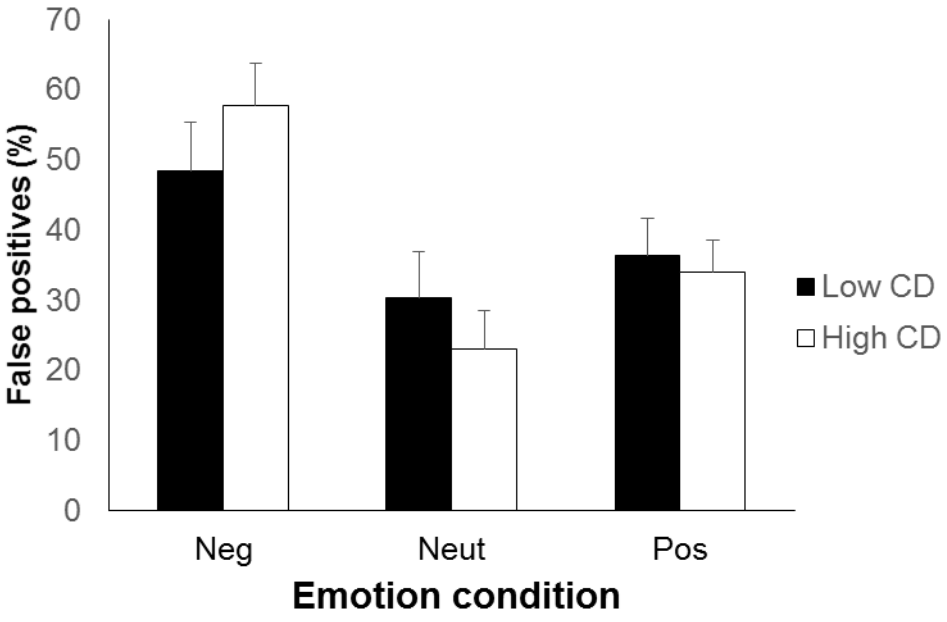

Figure 2. Mean false positive error rates for new-related items at each emotion condition for both cognitive disorganisation groups within the High estradiol group. Error bars are SEMs.

Knowledge corruption index for false recognition of new-related items

For the knowledge corruption index for new-related items, there was a significant main effect of Emotion ($F_{(2, 96)}$ = 24.34, p < .001. η_p^2 = .34). Post-hoc pairwise comparisons (Bonferroni) revealed that KCIs for the negative list were significantly higher compared to both the neutral and the positive lists (both p < .001). The neutral list also yielded lower KCIs compared to the positive list, but this did not reach significance (p = .09). Similar to the previous analysis, the Emotion × Estradiol group × CD group interaction was significant ($F_{(2, 96)}$ = 3.19, p = .04, η_p^2 = .06).

As in the previous analysis, the interaction was followed up with two 3 × 2 mixed model ANOVAs. For the Low estradiol group, the ANOVA revealed a significant main effect of Emotion ($F_{(2, 48)}$ = 13.78, p <.001, η_p^2 = .365). Pairwise comparisons showed there is a significantly higher KCI in the negative condition compared to both the neutral and the positive conditions (both p < .05). The between subject effect of CD also approached significance ($F_{(1, 24)}$ = 3.795, p = .06), with High CD participants yielding lower KCI scores than the Low CD group. Moreover, the interaction between Emotion and CD approached significance ($F_{(2, 48)}$ = 3.02, p = .058, η_p^2 = .112). The interaction was investigated using a series of t-tests, comparing the CD groups for each emotion. For the negative KCI and the positive KCI, the difference between the High and Low CD groups approached significance $t_{(24)}$ = 1.98, p = .06, and $t_{(24)}$ = 2.46, p = .021 respectively (see Figure 3A). The same ANOVA for the High estradiol group also yielded a main effect of Emotion ($F_{(2, 48)}$ = 11.05, p < .001, η_p^2 = .32), again with the negative emotion yielding a larger KCI than both the neutral and the positive conditions (both p < .05). In contrast to the Low estradiol group, the Emotion x CD interaction for the High estradiol group was not significant ($F_{(2, 48)}$ = 1.04, p = .362, η_p^2 = .04), as was the between subjects effect of CD (p = .74).

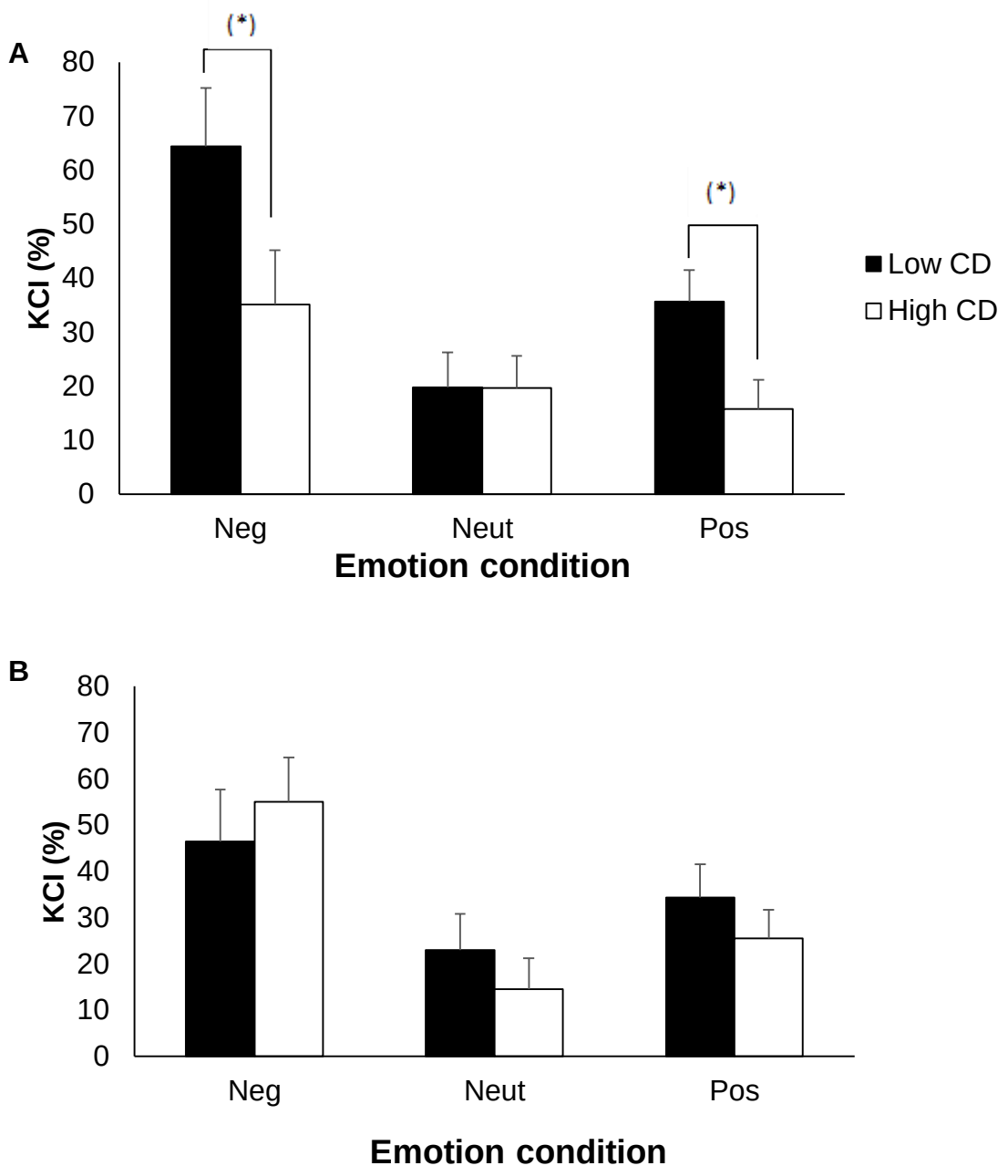

Figure 3. Mean knowledge corruption indices for new-related items at each emotion condition for both cognitive disorganisation groups within the Low (A) and High (B) estradiol groups. Error bars are SEMs, (*) = $p < .06$.

Discussion

The present study aimed to investigate whether individual differences in false memory rates and meta-memory ability for emotionally salient stimuli differed in women depending on menstrual cycle phase and estradiol levels. It was hypothesised that because memory is enhanced for emotional stimuli (and especially negative stimuli), a higher rate of false memories would be produced for the emotional word lists, compared to the positive ones. We also sought to investigate the effect of schizotypal traits on this effect. Moreover, given that estradiol was previously shown to influence memory and meta-memory in highly schizotypal participants (Hodgetts et al., 2015), we sought to investigate whether estradiol would still protect against false memories (and false memory overconfidence), despite the enhancing effects of emotion.

We found a significant effect of emotion for the false positive error rates and the knowledge corruption indices, for both the new-related words and the critical lures. As expected, the negative word lists produced more false memories, and a higher level of confidence in false memories, compared to both the neutral and the positive word lists. Moreover, a significant interaction between estradiol, cognitive disorganisation, and emotion was found for both the false positive error rates and the knowledge corruption indices for the new-related items. For the false positive error rates, this interaction was driven by an interaction between emotion and cognitive disorganisation in the High estradiol group only. However, there were no significant differences between the cognitive disorganisation sub-groups for any of the three emotion conditions. In contrast, for the knowledge corruption indices, the interaction was underpinned by an interaction between emotion and cognitive disorganisation in the Low estradiol group only. Specifically, highly disorganised participants were less confidence in their false memories compared to the less disorganised participants, for both the positive and negative word lists, when estradiol levels were low.

No estradiol-related improvement in (meta-) memory in highly schizotypal women

In addition to the two emotion conditions, the present study included a neutral condition in an attempt to replicate the finding of Hodgetts et al. (2015). Specifically, in this condition, highly disorganised participants, with a high level of estradiol, were predicted to show a reduction in false positive error rates and knowledge corruption, compared to those with low estradiol levels. The results showed that highly disorganised participants with a high level of estradiol produced lower false positive error rates and knowledge corruption indices compared to those with a low level of estradiol (23.81% vs. 22.96% and 19.65% vs. 14.56%, respectively).

However, these differences are not statistically significant. The two studies are largely similar in terms of design and samples; however, there are differences between the studies that may explain this result. Firstly, it should be noted that the false positive error rates and knowledge corruption indices in the present study are considerably smaller than those previously produced by Hodgetts et al. (2015). For example, the highly disorganised participants with low estradiol in the previous study produced false positive error rates and knowledge corruption indices of 38.62% and 32.70%, respectively. This is considerably larger than those produced by the highly disorganised participants with low estradiol in the current study (23.81% and 19.65%, respectively). Indeed, the false positive error rates produced by the highly disorganised participants with low estradiol in the present study are comparable to those produced by the highly disorganised participants with high estradiol in the previous study (25.00% and 21.34%, respectively). Therefore, one possible explanation for the results of the neutral condition in the present study is that the error rates produced by the highly disorganised participants were subject to a floor effect.

This is in line with an argument proposed by Hodgetts et al. (2015). There, it was noted that when highly disorganised participants did show an improvement in memory and meta-memory with a high level of estradiol, their "improved" error rates were comparable to those produced by participants with a low level of cognitive disorganisation. Consequently, it was suggested that the effect of estradiol on false memories and meta-memory is not enhancing per se, rather estradiol has a "normalising" effect. Thus, with respect to the present study, as the highly disorganised participants with low estradiol were able to produce a "normal" error rate, estradiol did not have a significant effect. However, it is unclear why the highly disorganised participants in the present study were able to produce lower error rates than those reported previously. It is possible that the overall lower sample size in the current study led to a smaller number of participants in the highly disorganised group with very high levels of cognitive disorganisation. Indeed, the highly disorganised/low estradiol participants in the previous study (n = 21, compared to n = 14 in the current study), yielded a slightly higher mean cognitive disorganisation score, compared to the current study (7.09 vs. 6.64). However, given that this difference is small, it is unlikely that a difference in cognitive disorganisation levels alone led to the smaller error rates in the current sample.

A further source of difference between the samples concerns the participants' hormone profiles. Although the same procedure was used to classify the highly disorganised participants as either high or low in estradiol, there are some differences between the two samples. Specifically, while both the previous and current highly disorganised/low estradiol groups had similar estradiol levels (1.69 pg/ml vs 2.04 pg/ml, respectively), there is a large difference in progesterone between the two groups, with the current sample yielded a considerably higher progesterone level than the previous sample (107.93pg/ml vs 76.91pg/ml, respectively). Indeed, Ertmann et al. (2011) demonstrated that a high level of progesterone during the luteal phase during encoding was associated with significantly better recall of emotionally salient

stimuli (emotional images). Therefore, it is possible that a higher level of progesterone in the highly disorganised participants in the present sample underpinned their superior performance compared to the previous analysis.

Interestingly, in the present study, participants with low schizotypy and low estradiol showed a greater degree of false memory confidence for emotional word lists than high CD participants with low estradiol levels. This is in direct contrast to what our initial prediction, that highly schizotypal participants with low estradiol should show the most confidence in their false memories. A possible explanation for this is that in highly schizotypal participants, it is the processing of emotion that is affected by the presence of cognitive disorganisation, and not (meta-) memory processes *per se*. Although the processing of emotion itself was not assessed in the present study, there is some evidence to suggest that the schizophrenia is associated with deficits of emotion processing. Indeed, a number of studies show that patients are generally less able to accurately label facial and vocal emotional cues, compared to healthy controls (Kohler et al., 2000; Maat et al., 2015; Murphy & Cutting, 1990). However, when estradiol is high, the highly schizotypal participants showed more false memory confidence than the low schizotypy participants, particularly for negative stimuli. This might suggest that estradiol facilitates emotional processing in the highly schizotypal participants, such that the expected effect of emotion on memory (more false memories, increased confidence) occurs. Whilst this is speculative, recent research has shown that estradiol is capable of modulating neural activity in brain regions associated with facial emotion processing in patients with schizophrenia (Ji et al., 2015).

Emotionality influences on false memories and meta-memory

The present study demonstrated a consistent effect of emotion on both the number of false memories participants produced, and their confidence in them. Specifically, for both the

false positive error rate and the knowledge corruption index, a higher number of false memories and a greater degree of false memory confidence was found for negative words, compared to both neutral and positive words. Moreover, neutral words produced the lowest number of false memories and the lowest degree of false memory confidence. Given that the effect of emotion occurred regardless of the participants' level of cognitive disorganisation, or estradiol, this suggests that the influence of emotionally salient stimuli on the processes underpinning false memory formation and meta-memory is greater than that of schizotypy or estradiol. This notion is supported by the observation that the false positive error rates and knowledge corruption indices for the critical lures were influenced by emotion, but not schizotypy or estradiol levels. This finding is in line with a number of previous studies showing that emotional stimuli, and particularly negative stimuli, can elicit a higher number of false memories than neutral stimuli (Brainerd et al., 2008; Gallo et al., 2009; van Damme & Smets, 2014) and consistent with the notion that emotion increases the conceptual similarity across items, leading to more false memories (Gallo et al., 2009). Although the neurological mechanism of emotional effects on false memory is yet to be directly investigated, Brainerd et al. (2008) suggest that emotional stimuli lead to increased medial temporal (MTL) activation, but reduced prefrontal cortical activity, which in turn, results in an increased false positive error rate. This suggestion, while speculative, is based on previous work suggesting that false positive responses to neutral stimuli are underpinned by increased MTL activity, and PFC-based retrieval monitoring can limit the formation of false memories (Schacter & Slotnick, 2004).

The effect of emotion was also consistently found for the knowledge corruption indices, reflecting a robust effect of emotion on meta-memory. Similar to the false positive error rates, a higher degree of false memory confidence was found for the negative word lists, relative to the neutral and positive lists. At present, the literature concerning emotion effects on meta-memory is limited. Moreover, those studies that do exist report varying results,

depending upon the meta-memory measure employed (Fairfield et al., 2015). Critically, to date, there have been no studies looking directly at the effect of emotion on retrospective confidence ratings (such as KCI). However, an integrative relationship between emotion processing and cognitive control is well-established (for a review, see Gray, 2004). Such studies have typically required participants to undertake a cognitive control task (such as the Stroop task, working memory tasks, or inhibitory control tasks) while processing task-irrelevant emotional stimuli. Consequently, a number of studies show that emotional stimuli have an interfering effect on cognitive control processes, leading to poor performance (Kensinger & Corkin, 2003; DeHouwer & Ribboel, 2010). These findings have been complimented by neuroimaging studies (Taylor et al., 2004; Sommer et al., 2008; see Mueller, 2011 for a review). For example, Sommer et al. (2008) demonstrated that negative mood was associated an increased working memory error rates (measured by the Simon task). This was accompanied by a reduction in lateral PFC activity, suggesting that PFC activity when completing a working memory task is sensitive to a negative mood state. Given that meta-memory processes are conceptually similar to cognitive control processes (Nelson & Narens, 1990), and associated with similar, prefrontal cortical regions (Do Lam et al., 2012), it may be that negatively valanced stimuli has a similar, interfering effect on meta-memory processes.

Emotion, estradiol, and schizotypy effects on false memories

Investigating false positive error rates revealed an interactive effect of emotion, estradiol and schizotypy. This was driven by an interaction between emotion and cognitive disorganisation in the High estradiol group only, although this was not statistically significant. While highly disorganised participants with relatively high estradiol levels produced more false memories than less disorganised participants for negative words, they produced fewer false memories for neutral and positive words. Furthermore, the difference between the neutral and the positive condition is small for highly disorganised participants with high estradiol.

However, additional analyses revealed that the difference between the schizotypy groups in this Estradiol group were not significant. It is interesting to note, that the false positive error rate (negative words) for highly disorganised participants with relatively low estradiol is much lower than those with higher estradiol levels (57.78% vs. 42.86%). Taken together, in contrast to our original hypothesis, this suggests that negative stimuli have a greater effect on false memory rates in highly schizotypal participants, particularly when estradiol is high.

Emotion, estradiol and schizotypy effects on meta-memory

The analysis of confidence in false memories, as measured by knowledge corruption indices, also revealed a significant interaction between emotion, estradiol and cognitive disorganisation. In contrast to the analysis of false positive error rates, this interaction was underpinned by an interaction between emotion and cognitive disorganisation in the Low estradiol group only. Further analysis revealed that when estradiol is low, the highly disorganised participants were less confident in their false memories compared to participants with low levels of cognitive disorganisation, for the negative and positive emotion conditions. Participants had a similar level of confidence in false memories for the neutral condition. There was no such interaction in the High estradiol group. The highly disorganised participants with relatively high estradiol show an increased KCI compared the Low estradiol group for the emotional lists, but this difference was not significant. There was no difference between the CD groups for the neutral lists, and this was stable with a high level of estradiol. Moreover, when estradiol is high, the highly disorganised group exhibit poorer meta-memory, while the less disorganised groups appear to improve. This results in no difference between the CD groups in meta-memory when estradiol is high.

In the previous study, estradiol was shown to improve meta-memory abilities specifically in highly schizotypal participants (Hodgetts et al., 2015). This selective enhancing effect of estradiol was explained in terms of individual differences in physiology between

participants with different levels of cognitive disorganisation. Specifically, it was argued that high levels of schizotypy are associated with a relative hyperdopaminergia, and a better ability to adapt to the higher dopamine levels associated with higher levels of estradiol levels. In turn, a high level of estradiol resulted in improved (meta-) cognitive performance. With respect to the present study, it might be argued that the combined effect of estradiol, emotion, and cognitive disorganisation on arousal, resulted in dopaminergic function that was over the optimal level for good cognitive performance. Consequently, highly schizotypal participants, with high estradiol levels performed particularly poorly in the emotional conditions. In contrast, those with a relatively low estradiol level have only the effect of emotion on their arousal levels, and thus, their performance is good. Critically, this does not explain why participants with low levels of schizotypy are much worse without estradiol.

Conclusions

In conclusion, in contrast to Hodgetts et al. (2015), the present study did not demonstrate an enhancing effect of estradiol on memory and meta-memory in highly schizotypal women. This may be due to differences in the number of false memories produced by the highly disorganised participants in the present study, or their considerably higher levels of progesterone. The present study did, however, consistently demonstrate an effect of emotion on both the number of false memories participants produced, and their confidence. Specifically, negative stimuli were associated with a higher number of false memories and greater false memory confidence compared to neutral and positive stimuli. This effect occurred regardless of participants' estradiol or schizotypy level. Moreover, regarding the number of false memories, the present study demonstrated that the effect of negative stimuli was particularly evident in highly schizotypal participants with high estradiol levels. In contrast, for memory confidence, highly disorganised participants were less confident in their false memories for both positive and negative stimuli, when estradiol was low. This may be due to the combined

effect of estradiol, emotion and schizotypy on dopaminergic activity, leading to over-arousal and in turn, poor performance. However, the relationship between these factors requires further investigation to determine the precise mechanism of this effect, and to further explain why less schizotypal participants produced a poorer performance with lower estradiol levels.

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Chapter 6

Preface

The previous chapters have demonstrated that sex hormones are capable of influencing cognitive abilities, such as those related to cognitive control and executive function. In addition, the previous chapters showed that sex hormones can modulate functional cerebral organisation at a behavioural level (demonstrated by the degree of lateralisation measured using dichotic listening tasks). However, what is not clear from these studies, is whether sex hormones exert such effects via an influence on task-related brain activity, or via an influence on resting state connectivity. Indeed, the influence of sex hormones on resting state activity, and how this might affect the stability of resting state networks, is currently a matter of debate within the larger neuroimaging literature (Arélin et al., 2015; De Bondt et al., 2015; Hjelmervik et al., 2014; Petersen et al., 2014). Thus, the aim of the study presented in the following chapter was to investigate menstrual cycle effects in two resting state networks relevant to the results presented in the previous four chapters.

Sex differences and menstrual cycle effects in cognitive and sensory resting state networks

Abstract

The stability, and test-retest reliability of resting state connectivity is currently under debate. That is, it not clear whether resting state connectivity reflects stable, structural characteristics of the brain, or is modulated by the psychological and/or physiological state of the participant during the scanning session. Given that previous research has demonstrated sex differences and sex hormonal effects in task-related activity, the present study aimed to investigate sex differences in two resting state networks. In light of previous studies suggesting that fluctuations in sex hormones can affect cognitive control and auditory-based behavioural tasks, the present study investigated the default mode network and the auditory network. Resting state fMRI was conducted in 19 healthy women, during three different menstrual cycle phases (menstrual, follicular, and luteal). Nineteen men underwent three resting state fMRI sessions at corresponding time intervals. Independent component analysis was used to identify the networks of interest. For the default mode network, the results showed that resting state connectivity was stable in men, but changed across the menstrual cycle in women. In contrast, no cycle effect was found for the auditory network. Instead, a sex difference was found, with men showing increased connectivity compared to women. It is concluded that the effect of sex hormones on cognitive tasks are driven by their effect over task-related activity. Moreover, the findings suggest that cognitive resting state networks might be less stable than sensory-based networks.

Introduction

Sex differences have been demonstrated in both brain structure and function (for reviews see McEwen, 2001; Cosgrove et al., 2007). For example males, on average, have a larger overall brain volume as well as larger volumes in specific regions such as posterior cingulate gyri, precuneus, and the hippocampus as compared to women. In contrast, women generally have larger volumes in the planum temporale, anterior cingulate cortex, and lateral occipital cortex (for a recent review and meta-analysis, see Ruigrok et al., 2014). Moreover, numerous studies have demonstrated sex differences in specific cognitive tasks, with men outperforming women in tests of spatial ability (Linn & Petersen, 1985; Voyer et al., 1995), and women outperforming men in tests of verbal ability (Hyde & Linn, 1988). Notably, these processes are lateralised in the brain, with verbal processes/language being lateralised to the left hemisphere, and visuospatial processes to the right. Subsequently, further behavioural studies have shown sex differences in laterality, with men typically being more strongly lateralised than women (Hausmann & Güntürkün, 1999; Hausmann et al., 1998; Shaywitz et al., 1995; but see Sommer et al., 2004). This finding has since been supported by a range of neuroimaging studies (Kansaku & Kitazawa, 2001).

Sex differences in functional brain organisation partly result from transient activating effects of these hormones (such as during the menstrual cycle) that occur throughout the lifespan (Luine, 2014). For example, a recent behavioural study of functional brain organisation using a consonant-vowel dichotic listening task (Hodgetts et al., 2015a, see Chapter 2) demonstrated that high levels of estradiol and progesterone were associated with a reduction in language lateralisation, regardless of cognitive demands. As such, it was concluded that sex hormones influence functional brain organisation via an effect on task-related (stimulus-driven/bottom-up) activity (see also Cowell et al., 2011; Hampson, 1990a,b; Hausmann & Güntürkün, 2000; Hausmann et al., 2006; Hausmann et al., 2013; Wadnerkar et al., 2008; Weis

et al., 2008; Weis et al., 2011). Additional behavioural and neuroimaging studies have shown that sex hormones can improve some cognitive (and meta-cognitive) abilities (Hjelmervik et al., 2012; Joffe et al., 2006; Keenan et al., 2001; Maki et al., 2002). For example, Hodgetts et al. (2015b, see Chapter 4) demonstrated that high levels of estradiol can improve memory and meta-memory abilities in highly schizotypal participants.

A number of behavioural studies have shown that estradiol and progesterone can modulate cerebral lateralisation, via their influence on interhemispheric transmission. Specifically, during the follicular and/or luteal phase, with high levels of estradiol or estradiol and progesterone respectively, women are typically less lateralised relative to the low-hormone menstrual phase (e.g., Alexander et al., 2002; Altemus et al., 1989; Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Sanders & Wenmoth, 1998), probably due to a hormone-modulated reduction in functional connectivity between the two hemispheres (Hausmann et al., 2013; Weis et al., 2008, 2011). Additional studies using task-related fMRI have shown that functional connectivity is susceptible to sex hormone fluctuations across the menstrual cycle (e.g. word-matching task, Weis et al., 2008; figure comparison, Weis et al., 2011). Furthermore, sex hormones, especially estradiol, have been shown to affect performance in frontally mediated cognitive tasks, such as top-down attention control (Hjelmervik et al., 2012), response inhibition (Marinho et al., 2008) and working memory (Jacobs & D'Esposito, 2011; Keenan, 2001).

Recent fMRI research has revealed several functionally relevant cortical networks that exhibit synchronous fluctuations in brain activity while participants are not undertaking a specific task. These studies have shown that the brain exhibits a pattern of low-frequency oscillations in the BOLD signal (approx. 0.01-0.1Hz, Damoiseaux et al., 2006) while the participant is at rest, which then increases during the relevant cognitive or sensory process. The so-called resting state fMRI (rs-fMRI) approach was initially described by Biswal et al. (1995),

who demonstrated temporally correlated time courses of low frequency fluctuations within the sensorimotor cortex during rest. Subsequent research using rs-fMRI has identified a number of networks that are spatially comparable to task-related activations (Damoiseaux et al., 2006), such as executive function (Laird et al., 2011; Seeley et al., 2007), language (Laird et al., 2011; Tie et al., 2014) and memory (Laird et al., 2011; Vincent et al., 2006) resting state networks. These networks are distinct from the default mode network (DMN), which is comprised of the posterior cingulate cortex (PCC)/precuneus, lateral parital cortex, and the dorsal and ventral medial prefrontal cortex (mPFC) (Fox et al., 2005; Greicius et al., 2003; Laird et al., 2011). The DMN is shows higher activity levels during rest, which is differentially attenuated during tasks, according to task demands (Fox et al., 2005; Raichle et al., 2001; Raichle, 2015). As such, the function of this network was initially hypothesised to be stimulus-independent thought (e.g. daydreaming, mind-wandering) and 'spontaneous cognition' (e.g. thinking about the past/future) (Andrews-Hanna et al., 2010; Christoff et al., 2009). More recently, it has been suggested (Raichle, 2015) that resting state activity in the DMN simply reflects spontaneous activity in brain, a "much more fundamental role" (p. 440) than spontaneous cognition. Furthermore, hyperconnectivity and hyperactivity in the DMN has been demonstrated in psychiatric disorders, such as schizophrenia (Whitfield-Gabrieli et al., 2009). In addition to cognitive resting state networks, a number of sensory resting state networks have been identified, including sensorimotor, visual, and auditory networks (Laird et al., 2011).

Due to the unrestricted nature of resting state fMRI, the degree of variability in resting state connectivity is currently under debate. Specifically, it is unclear whether resting state reflects trait-like structural characteristics of the brain, or is dependent on the psycho- and/or physiological state of the participant during scanning. Evidence to date has yielded mixed results. For example, some studies have provided evidence for the former notion by demonstrating a link between resting state functional connectivity and anatomical connectivity

via white matter pathways (Johnston et al., 2008), including in the DMN (Van Den Heuvel et al., 2009). Further studies have shown resting state to be consistent across both multiple test sessions (Damoiseaux et al., 2006) and multiple test sites (Biswal et al., 2010), with medium (Braun et al., 2012; Guo et al., 2012) to high (Zuo et al., 2010) test-retest reliability. In contrast, a number of studies suggest that resting state is variable according to time of day (Blautzik et al., 2013) or psychological factors, such as mood (Harrison et al., 2008), learning (Zhang et al., 2014) or prior task execution (Pyka et al., 2009; Waites et al., 2005).

A recent suggestion is that resting state connectivity, like task-related connectivity, may be influenced by sex hormones (Arélin et al., 2015; De Bondt et al., 2015; Hjelmervik et al., 2014; Petersen et al., 2014). This is a critical question given that, as previously mentioned, a number of studies have demonstrated an association between sex hormones and task-related brain activity. However, an open question remains regarding whether such hormone effects are task-related, or due to an influence on resting state functional connectivity.

Several lines of evidence support the notion that resting state may be affected by fluctuations in sex hormones. A number of recent studies have investigated sex differences in rs-fMRI, albeit with inconsistent results. For example, while Weissman-Fogel et al. (2010) did not demonstrate any sex differences in functional connectivity in the DMN, salience, and fronto-parietal networks, other studies suggest that such sex differences are present (Biswal et al., 2010; Filippi et al., 2013; Hjelmervik et al., 2014; Tian et al., 2011). A study using a large sample of participants (N = 603) by Allen et al. (2011) revealed stronger functional connectivity in the DMN in females, but no sex difference in the fronto-parietal network. Filippi et al. (2013) demonstrated increased functional connectivity in men in parietal and occipital networks, while women showed increased functional connectivity in frontal and temporal regions. Similarly, Hjelmervik et al. (2014) reported higher functional connectivity in women in two fronto-parietal networks. Such sex differences in resting state connectivity

are likely to be a reflection of differences in brain structure. Moreover, the findings of sex differences in resting state for frontal and parietal regions are somewhat similar to those demonstrated using task-related fMRI during visuo-spatial processing, where men demonstrated increased activity in parietal regions while women typically activate prefrontal regions (Jordan et al., 2002). Therefore, it is possible that sex differences in resting state activity might partly underlie sex differences in task-related activity, and in turn, behaviours underpinned by these regions.

Critically, results to date are inconsistent and this might be due to methodological differences between resting state studies. For example, Bluhm et al. (2008) demonstrated that sex differences were revealed inconsistently, depending on the analytical method used. Furthermore, it is possible that sex differences are limited to specific resting state networks. Indeed, Filippi et al. (2013) suggest that sex differences are more apparent in cognitive as opposed sensory resting state networks. Consequently, these authors suggest that sex differences in functional connectivity between cognitive resting networks and several frontal regions (such as cingulate cortex, dlPFC, and inferior frontal gyrus) may be related to sex differences in task-related activity during processes such as working memory, emotion regulation, and selective attention.

To date, there have been only very few studies investigating sex hormonal effects functional connectivity in the resting state. Critically, there is significant heterogeneity across these studies, both in terms of methodology and results. Petersen et al. (2014) adopted a between-subjects design to investigate resting state functional connectivity in the DMN (anterior section only) under different hormonal conditions, both across the menstrual cycle in normally cycling women, and in oral contraceptive pill users. This study demonstrated increased functional connectivity between the right anterior cingulate cortex (ACC) and the executive control network, and reduced functional connectivity between the left angular gyrus

and the anterior DMN during the luteal as compared to the menstrual phase (termed ‘early follicular’ by the authors). However, in this study, women in the menstrual phase had very high progesterone levels, resulting in a small difference between the cycle groups. Moreover, no cycle difference in estradiol was found, suggesting that the women in this study were inaccurate in their cycle phase self-report (see also Gordon et al., 1986). As such, these results might be due to other individual differences between participants (e.g. personality traits), especially since a between-subjects design was used. Hjelmervik et al. (2014) investigated four fronto-parietal (cognitive control) resting state networks in a repeated measures design. While this study did not find any cycle-related effect on functional connectivity, sex differences were revealed in two networks. In the anterior fronto-parietal network, women showed greater functional connectivity in the left middle frontal gyrus (MFG), bilateral precuneus, and right inferior parietal lobe. In the right dorsal network, women showed higher connectivity in the left cerebellum. De Bondt et al. (2015) also did not find any effect of sex hormones in fronto-parietal networks (termed ‘executive control networks’ by the authors). However, in the DMN, an increase in functional connectivity between the network the cuneus was found in the luteal phase, as compared to the follicular phase. Finally, Arélin et al. (2015) conducted 32 resting state scans in a single subject across four menstrual cycles. Initial analyses using eigenvector centrality revealed that high progesterone levels were associated with increased connectivity of the dorsolateral prefrontal cortex (dlPFC) and the sensorimotor cortex to the resting state network. A further, region-of-interest analysis revealed that high progesterone levels were associated with higher functional connectivity between right dlPFC, bilateral sensorimotor cortex, and the hippocampus, as well as between the left dlPFC and bilateral hippocampi during rest. A potential explanation for these differing findings is that this study differed in its analytic approach (i.e., eigenvector centrality and ROI analysis as opposed to ICA), and consequently, does not identify specific resting state networks.

The present study investigates sex and sex hormonal effects on functional connectivity in both a cognitive (DMN) and a sensory (auditory) resting state network. The DMN was selected as previous studies have demonstrated sex differences in functional connectivity for this network (Allen et al., 2011; Fillipi et al., 2013, but see Weissman-Fogel et al., 2010). Moreover, in contrast to Petersen et al. (2014), the present study will investigate the whole DMN as opposed to only the anterior portion. In addition, previous behavioural and task-related fMRI evidence suggests that regions of the DMN might be affect by hormonal fluctuations. As previously mentioned, Hodgetts et al. (2015b) demonstrated that high levels of estradiol are associated with improvements in meta-memory ability, albeit in highly schizotypal women only. Given that Do Lam et al. (2012) demonstrated that meta-memory processes are linked to regions of the DMN, such as medial PFC, orbitofrontal cortex, and anterior cingulate cortex, it follows that functional connectivity in the DMN might be modulated by hormonal fluctuations.

The auditory network was selected as a number of studies using auditory tasks, such as the dichotic listening paradigm, have demonstrated sex hormone effects on functional brain organisation (Cowell et al., 2011; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008; Hodgetts et al., 2015a). However, it is currently unclear whether these effects are due to hormonal effects on task-related activity, or if they were partly dependent on changes to resting state functional connectivity.

Thus, the aim of the present study was to investigate sex differences and menstrual cycle effects in both the DMN and the auditory resting state network. In line with previous resting state (Petersen et al., 2014) and behavioural studies in the same cohort (Thimm et al., 2014), we predicted hormone-related fluctuations in the DMN between the follicular/luteal phase and the menstrual phase. In addition, on the basis of a recent study suggesting that hormonal effects in dichotic listening are stimulus-driven (Hodgetts et al., 2015a; Chapter 2), we expected resting state connectivity in the auditory network to be stable across the cycle.

Method

Participants

Nineteen healthy women (out of 21 originally tested, see hormone assay section for exclusion criteria) with a mean age of 24.73 years (*SD* = 3.58; range: 18 – 34 years) and 19 healthy men with a mean age of 24.05 years (*SD* = 2.72; range 20 - 29) completed three sessions of resting state fMRI. Age did not differ between the sexes ($t_{(36)} = 0.66$, $p = .51$).

The data presented in this study were collected in Aachen, Germany (University Hospital, RWTH Aachen University) as part of a larger fMRI study of functional brain organisation across the menstrual cycle (Thimm et al., 2014). Resting state data was analysed at Durham University. All participants were native German speakers. All participants consistent right-handers according to the Edinburgh Handedness Inventory (female LQ = 84.15, *SD* = 13.20; male LQ = 86.19, *SD* = 11.09). Handedness did not differ between the sexes ($t_{(36)} = 0.52$, $p = .61$). Women who had taken hormonal contraceptives or other hormone regulating medications during the previous 6 months were excluded.

The women were tested in three different cycle phases: the menstrual phase (cycle days 1 - 3), follicular phase (cycle days 10 - 12) and luteal phase (cycle day 20 - 22). Time points for each session were estimated according to self-reported menstruation onset, and took individual average cycle length into account. To control for a possible session effect, testing order was randomised across subjects such that all three cycle phases were equally distributed across the three time points. Men were tested three times with one to two weeks in between two testing sessions and were subsequently assigned into three groups, equivalent to the female cycle phases. To control for circadian influences on hormone levels, every experimental session was performed at the same time of day.

Hormone assays

Blood samples were taken from all women immediately before the test session. Estradiol and progesterone levels were assessed via electrochemiluminescence immunoassay to verify cycle phase. Luteal progesterone levels were used an indication of ovulation for each women. As a result, two women were excluded from further analysis. Of the 19 women included, six began testing in their menstrual phase, eight in their follicular phase, and five in their luteal phase.

Resting state fMRI

Functional magnetic resonance imaging was performed on a 3-Tesla Phillips Systems Achieva scanner, using an eight-channel SENSE head coil and T2*-weighted axial EPI sequences. Each run comprised 250 scans (plus three initial dummy scans) with the following parameters: number of slices: 37 continuous slices parallel to the AC–PC line comprising the whole brain; slice thickness: 3 mm; no interslice gap; matrix size: 64 × 64; field of view: 192 ×192 mm; echo time: 30 ms; repetition time: 2500 ms; flip angle: 81°.

Participants were instructed to relax with their eyes closed during scanning. In addition to the resting state scans, two attention tasks were administered (see Thimm et al., 2014), however, resting state data was always acquired first.

Data analysis

The data were pre-processed using SPM 8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/) implemented in MATLAB 2013b (The Mathworks Inc., Natick, MA, USA). After discarding the first three volumes (dummy scans), functional images were realigned to the first scan to correct for head movement. Unwarping was used to correct for the interaction of susceptibility artefacts and head movement. Volumes were normalized to a

standard EPI template based on the Montreal Neurological Institute reference brain using default settings for normalization in SPM8 with 16 nonlinear iterations. Finally, all images were smoothed with a Gaussian kernel of 8-mm full-width half-maximum.

GIFT (Group ICA of fMRI Toolbox; v1.3i/2.0e) was used to conduct group level Independent Component Analysis (ICA), employing default settings. Firstly, individual data dimensionality was reduced using principal component analysis (PCA) on each participant, separately. The data were then group concatenated and subjected to two further PCA data reduction steps. Secondly, the infomax algorithm was used to estimate forty independent components from the reduced data. Thirdly, back-reconstruction of individual spatial maps from the components estimated at group level was conducted using GICA. The values of each individual map and time courses were scaled to represent percent signal change. No temporal filtering was applied on the data in GIFT.

Spatial sorting was used to identify the networks of interest from the forty components. The default mode and auditory networks were identified via spatial sorting and statistical comparison to the intrinsic connectivity networks (ICNs) described by Laird et al. (2011). The component identified as the DMN (Figure 1a) correlated primarily with Laird et al.'s ICN 13 (r = 0.397). This component is comprised of mPFC, PCC and the precuneus. Laird et al. note that this component is strongly associated with theory of mind tasks, as well as episodic recall, imagining scenes and fixation. The component identified as the auditory network (Figure 1b) correlated primarily with Laird et al.'s ICN 16 (r = 0.356). This component is comprised of the primary auditory cortices, and is strongly associated with music and speech perception, as well as tone and pitch discrimination (Laird et al., 2011).

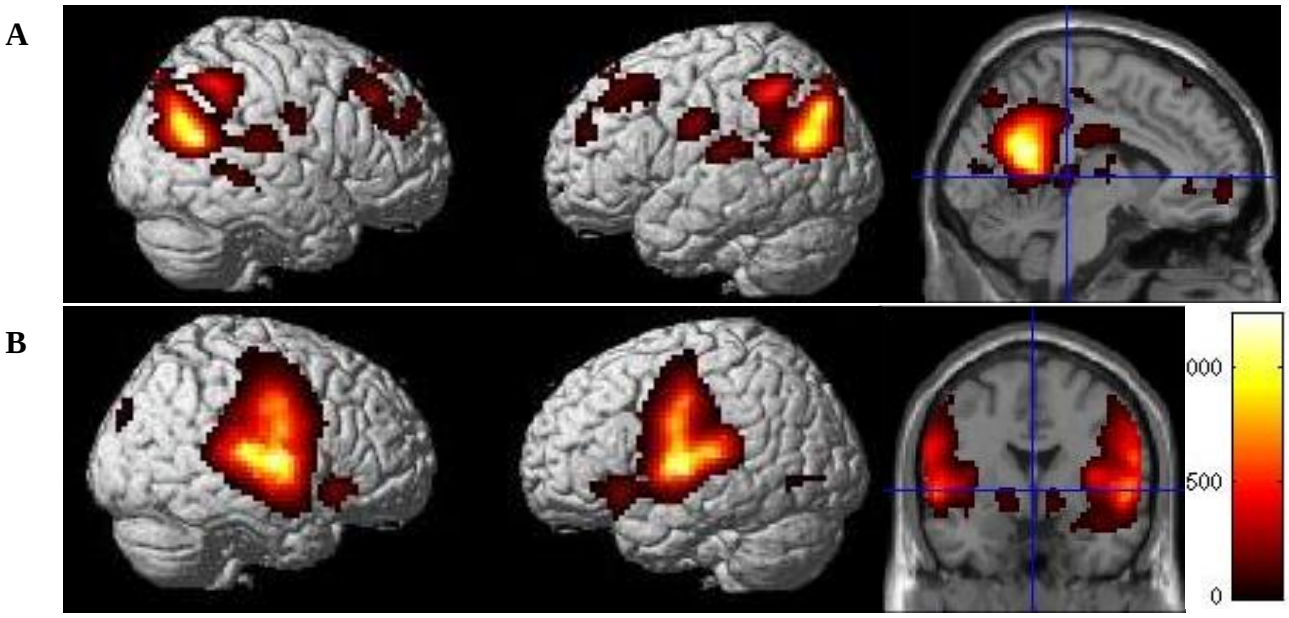

Figure. 1 Maps of the default mode (A; left, right and sagittal views) and auditory (B; left, right and coronal views) networks used in further analysis.

Group analyses of the spatial maps of both components were estimated using the individual back-reconstructed components to investigate whether changes in connectivity between the networks of the components and the rest of the brain varied according to sex or cycle phase. As the spatial maps represented the whole brain, the analysis estimates statistical parameter maps both for voxels within the core region of the component, as well as for those in distant, non-core regions. A 2 (Sex) × 3 (Cycle Phase) ANOVA was carried out for both components, using the full factorial design, with Sex specified as being independent and of unequal variance and Cycle Phase specified as dependent and of equal variance. The results were explored at a significance threshold of $p < 0.001$, uncorrected for multiple testing. To ensure that movement did not affect the results, individual alignment parameters were characterised by calculating four estimates of movement provided by van Dijk et al. (2012): mean translation, maximum translation, total translation, and mean rotation. Mean translation and mean rotation were included as covariates in the ANOVAs. Estimates of individual brain volume were calculated from tissue probability maps in subject space, from each participant's

structural T1 image using unified segmentation and normalisation routines in SPM8, and included as a covariate in the analysis.

A Monte-Carlo simulation of the brain volume was employed to establish an appropriate voxel contiguity threshold (Slotnick et al., 2003). This correction has the advantage of higher sensitivity, while still correcting for multiple comparisons across the whole brain volume. Assuming an individual voxel type I error of $p < 0.001$, a cluster extent of 17 contiguous resampled voxels was indicated as necessary to correct for multiple voxel comparisons across the whole brain at $p = 0.05$ (based on 10,000 simulations).

Results

Hormone concentrations

Hormone concentrations for each cycle phase are given in Table 1. A repeated measures ANOVA for estradiol revealed a significant effect of cycle phase ($F_{(2, 36)} = 22.55$, $p < .001$, $\eta_p^2 = .56$). Bonferroni-corrected post-hoc tests revealed significant differences between the menstrual and follicular phase ($p = .002$), the menstrual and luteal phase ($p < .001$), and between the follicular and luteal phase ($p = .03$).

The same analysis for progesterone also revealed a significant cycle phase effect ($F_{(1.003, 18.05)} = 35.44$, $p < .001$, $\eta_p^2 = .663$). Bonferroni-corrected post-hoc tests revealed a significant difference between the menstrual and luteal phase ($p < .001$), and between the follicular and luteal phase ($p < .001$).

Table 1. Means, standard deviations, and range (in parentheses) of estradiol and progesterone levels from blood samples of the female sample for each cycle phase.

	Menstrual	**Follicular**	**Luteal**
Estradiol (pmol/l)	104.53 ± 64.35 (25.80 – 252.00)	336.87 ± 270.95 (62.10 – 967.00)	500.84 ± 316.69 (238.00 – 1460.00)
Progesterone (nmol/l)	2.08 ± 0.91 (1 – 4.40)	1.89 ± 0.79 (0.9 -3.5)	32.74 ± 22.06 (8 -81.50)

Default mode network

The ANOVA revealed a significant interaction between Sex and Cycle phase. In women, a region of left prefrontal cortex (-36, 26, 22, cluster size = 33 voxels) showed increased connectivity with the default mode network during the menstrual phase, as compared to the follicular and the luteal phase (see Figure 2). No significant differences were found across repeated sessions in men. In addition, no main effect of Sex or Cycle phase/session was found.

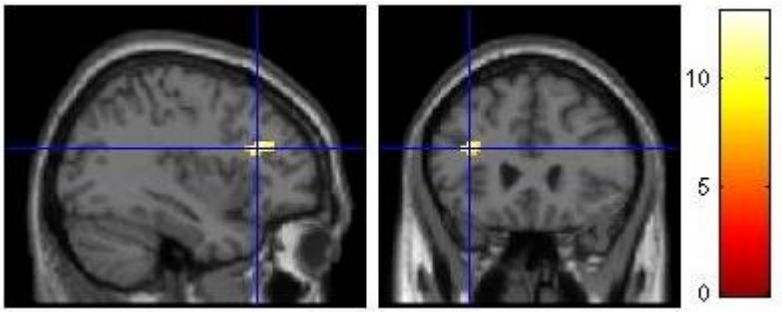

Figure 2. Sex × Cycle phase interaction effect on functional connectivity in the default mode network. Results are corrected for multiple comparisons ($p < 0.05$). Yellow blobs represent areas of higher connectivity in the left prefrontal cortex for women in the menstrual phase relative to the follicular and luteal phases.

Auditory network

The same analysis revealed a significant main effect of Sex, with a region of superior temporal gyrus (-54, 2, 1, cluster size = 53) and the postcentral gyrus (-36, -40, 58, cluster size = 43) showed increased connectivity with the network in men relative to women (see Figure 3). No main effect of Cycle phase/session and no interaction was found.

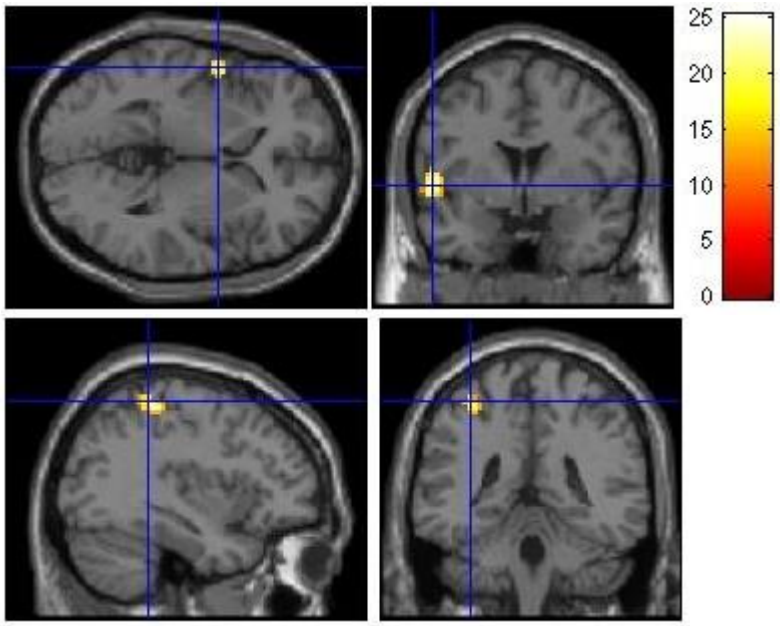

Figure 3. Sex difference in auditory network functional connectivity. Results are corrected ($p < 0.05$). Yellow blobs represent areas of higher connectivity in males, relative to females, in the superior temporal gyrus (A: -54, 2, 1) and in the post-central gyrus (B: -36, -40, 58)

Discussion

The present study investigated sex differences and sex-hormone effects in the default mode and auditory resting state networks. In the DMN, functional connectivity was stable across repeated testing sessions in men but changed across the menstrual cycle in women. Specifically, during the menstrual phase, women showed increased functional connectivity between a region of left frontal cortex and the DMN. No main effect of sex was found. In contrast, a sex difference was found in the auditory network. Here, men showed increased functional connectivity between the superior temporal gyrus, the postcentral gyrus, and the auditory network compared to women. However, no change in functional connectivity occurred across the menstrual cycle in women, or across testing sessions in men.

Menstrual cycle effect on default mode network

The present study demonstrates that resting state connectivity can be influenced by the natural fluctuations in estrogen and progesterone levels that occur across the female menstrual cycle. This finding has several implications for further neuroimaging studies, both task-related fMRI and rs-fMRI. Firstly, regarding the stability of rs-fMRI, this finding suggests that the test-retest reliability of resting state functional connectivity, at least for the DMN, is sex dependent. Specifically, the present study suggests that resting state functional connectivity of the DMN is stable in males only. In contrast, in women, the reliability of DMN functional connectivity is confounded by the effect of hormonal fluctuations across the menstrual cycle. However, this study focussed on only one cognitive network, and as such, this finding cannot be generalised to other cognitive resting state networks. Indeed, previous studies investigating other cognitive networks (e.g. fronto-parietal networks, Hjelmervik et al., 2014) reported no menstrual cycle effects. This might suggest that the stability of resting state functional connectivity is not only sex dependent but also network dependent.

The finding of a menstrual cycle effect on DMN resting state also has implications for previous findings from behavioural studies. Specifically, the present findings suggest that sex hormone effects on behaviours underpinned by regions of the DMN might be dependent on intrinsic functional connectivity as opposed to task related activity. For example, the previous finding of an estradiol-related enhancement of meta-memory ability in highly schizotypal women (Hodgetts et al., 2015b) may be underpinned by cycle effects on the DMN, especially as there is overlap in the regions involved (Do Lam et al., 2012). Indeed, several studies suggest that DMN deactivation is required for successful task performance (‘default mode interference’, Weissman et al., 2006; for a review, see Sonuga-Barke & Castellanos, 2007). For example, Weissman et al. (2006) investigated the relationship between task-related brain activity, resting state activity in the DMN, task-related deactivation of the DMN, and task

performance. Using a selective attention task, this study showed that poor performance was associated with reduced task-related activity in ACC and right prefrontal cortex, as well as less deactivation of the DMN. The authors suggest that this reflects a less efficient suspension of task-irrelevant cognitive processes (such as daydreaming), which in turn, interferes with task-related activity. Together with the present study (and Hodgetts et al., 2015b, Chapter 3), this might suggest that high levels of sex hormones (as present in the luteal and follicular phase) results in less connectivity of prefrontal regions to the DMN. Thus, these regions are available to be recruited during task-related activity, resulting in better task performance.

The finding of a sex hormonal effect on connectivity in the DMN might be of clinical relevance. Indeed, altered DMN connectivity is found in numerous psychiatric disorders, including those shown to be sensitive to hormone fluctuations or aberrant hormone levels. For example, it has been shown that schizophrenia is associated with atypical DMN activity. Whitfield-Gabrieli et al. (2009) demonstrated increased functional connectivity between mPFC and the DMN in patients and first-degree relatives, both at rest and during working memory tasks. Moreover, patients demonstrated hyperactivity in the DMN (reduced task-related suppression), and this was related to impaired memory performance. In addition, not only is schizophrenia associated with an aberrant hormonal profile (e.g. hypestrogenism in female patients; Bergemann et al., 2005), psychotic symptom severity has been shown to fluctuate in line with hormonal changes across the menstrual cycle (Riecher-Rössler et al., 1994; Seeman & Lang, 1990). This allows speculation on whether altered DMN connectivity, due to fluctuations and/or lower hormone levels generally, might affect processes underpinned by these regions (e.g. self-referential processes; Andrews-Hanna et al., 2010; Christoff et al., 2009). If so, this could potentially lead to the development of symptoms that might be characterised impaired self-referential processes and, possibly, altered DMN connectivity (e.g. delusional ideation).

In line with previous research (Petersen et al., 2014), an increase in functional connectivity with the DMN was found during the menstrual phase. However, the present study demonstrated increased connectivity between the DMN and a region of left frontal cortex while Petersen et al. (2014) showed increased connectivity between the right ACC and the DMN during this phase. Given that Petersen et al. (2014) employed a between-subjects design, it is possible that their findings reflect individual differences between the groups, as opposed to hormonal effects, especially as there was relatively small differences in estradiol and progesterone levels between the groups. However, as participants did not differ on basic demographic characteristics (e.g., age, education level), and no other participant characteristics were reported (e.g., mood, personality traits), this suggestion is highly speculative. Nonetheless, taken together, these findings suggest that cycle phase may be important to consider when investigating sex differences in the DMN.

The findings from the present study can also be linked to those reported by Thimm et al. (2014), as both studies involve the same participants (although two additional participants were excluded in the present study), and data from the same scanning session. As such, the present finding suggests that the cycle effect on selective attention reported by Thimm et al. (2014) might be due partly to hormonal effects on resting state as opposed to task-related activity. It is of interest to note that the region of left middle frontal gyrus showing increased connectivity to the DMN in the menstrual phase of the present study is similar to that highlighted in the PPI analysis of Thimm et al. (2014). Specifically, Thimm et al. (2014) reported that a region of left middle frontal gyrus yielded a stronger negative correlation with a region of left medial frontal gyrus during the menstrual phase. It is possible that together these findings might reflect DMN interference, with the left middle frontal gyrus being more connected to the DMN during the menstrual phase, and thus, less connected to the left medial

frontal region during task-related activity. However, as this was not directly tested in the present study, this suggestion is speculative.

Sex differences in the auditory resting state network

In contrast to the DMN, a similar analysis of the auditory network revealed a sex difference, with men showing higher connectivity between regions of the network and left superior temporal gyrus, and left postcentral gyrus. Fillipi et al. (2013) also demonstrated a sex difference in the auditory resting state network, with men showing higher connectivity between the network and the left insula and right cuneus. In contrast, women showed higher connectivity between the network and the left middle frontal gyrus. While this finding contrasts those of the present study, where no regions of increased connectivity were found in women, it should be noted that this result did not survive grey matter volume correction, as was applied throughout the present analysis.

The lack of menstrual cycle effect on the auditory resting state network has several implications. This suggests that the previously observed hormonal effects on auditory-based tasks, such as dichotic listening (e.g. Hodgetts et al., 2015a, Chapter 2; Cowell et al., 2011; Wadnerkar et al., 2008) are probably due to a hormonal influence on task-related activity, as opposed to underlying intrinsic functional connectivity. Moreover, the present study suggests that sex differences in sensory resting state connectivity (at least in the auditory network) occur independently of female hormonal state at the time of testing. One implication might be that the present finding is a reflection of structural differences between males and females. For example, Schlaepfer et al. (1995) demonstrated greater grey matter volume in the STG of women compared to men. Furthermore, Good et al. (2001) revealed greater grey matter volume specifically in the left STG of women as compared to men. A further study (Hsu et al., 2008) employed diffusion tensor imaging (DTI) to investigate sex differences in white matter

microstructure in this region. This study revealed lower fractional anisotropy in the right STG in women. However, the functional relevance of this is unclear. Regarding the left postcentral gyrus, Im et al. (2006) demonstrated greater cortical thickness in women compared to men. However, sex differences in white matter structure of this region are yet to be investigated. Further studies combining resting connectivity with measures of structural connectivity, such as DTI, may help address this issue (e.g. Greicius et al., 2008) and shed light on the mechanisms underlying sex differences in resting state connectivity.

Sex hormone effects in cognitive as opposed to sensory networks

In light of the lack of menstrual cycle effects in their study, Hjelmervik et al. (2014) suggested that rs-fMRI is less sensitive to hormone fluctuations than task-related fMRI. However, the present study does not support this, as functional connectivity in the DMN changed across the menstrual cycle in women. Instead, findings from the present study might suggest that resting state stability varies not only between the sexes, but potentially between networks with sensory networks proving more stable than cognitive networks. Given that the DMN and other cognitive networks (such as the executive control network and salience network) predominantly involve prefrontal areas (including medial PFC, dorsolateral PFC, orbitofrontal cortex, and anterior cingulate), it may be that these networks are more susceptible to cycle effects due to their higher sensitivity to hormonal actions. Indeed, physiological evidence suggests that prefrontal regions have particularly high estradiol levels as compared to other cortical regions, including parietal, temporal and cingulate cortices (Bixo et al., 1995) and a large number of estrogen receptors (Montague et al., 2008). Moreover, evidence from task related fMRI (Jacobs & D'Esposito, 2011; Joffe et al., 2006) and behavioural studies (Keenan et al., 2001; Hjelmervik et al., 2012) suggests that the prefrontal cortex is a key target for estrogenic activity in the cortex, and an important site for estrogenic effects on cognition. In contrast, sensory networks appear to be less affected by hormones, but more susceptible to

sex differences in brain structure. This might suggest that sex hormone effects on cognitive performance and/or functional brain organisation, at least for auditory-based tasks such as dichotic listening, are due to sex hormone effects on task-related brain activity and not due to changes in underlying sensory activity. Critically, the present study investigated only one cognitive and one sensory network. In addition, as previously described, Hjelmervik et al. (2014) did not find any cycle-related effects in four cognitive control networks. This might suggest that while cognitive networks are more susceptible to hormonal fluctuations across the cycle, the effect is restricted to specific networks, such as the DMN.

Conclusion

In conclusion, the present study demonstrated that functional connectivity in the default mode network is susceptible to hormonal fluctuations across the menstrual cycle in women, but stable across repeated testing sessions in men. This suggests that presence of a sex difference in this network might partly depend upon the hormonal status of women during the testing session. Moreover, these findings suggest that hormonal effects on tasks related to this network (e.g. meta-memory, cognitive control) might, at least in part, be based on task-independent functional connectivity as opposed to task-related activity. In contrast, functional connectivity in the auditory resting state network was stable in both men and women. However, a sex difference in functional connectivity was found in this network, possibly reflective of structural sex differences in the superior temporal and postcentral gyri. This finding supports the conclusions drawn previously (Hodgetts et al., 2015a, Chapter 2), that the effects of sex hormones on language lateralisation (in auditory-based tasks such as dichotic listening) are due to hormonal effects of task-related (stimulus-driven) activity, as opposed to intrinsic resting state connectivity. Finally, taken together, these results suggest that cognitive resting state networks may be more sensitive to hormonal fluctuations than sensory resting state networks.

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Chapter 7

General Discussion

The present thesis aimed to investigate the neuromodulatory effects of gonadal steroid hormones, such as estradiol and progesterone, with a focuson functional brain organisation and executive function ability. This was done across a series of studies using a range of behavioural paradigms, as well as resting state fMRI, in young, naturally cycling women.

Sex hormones, lateralisation and cognitive control

Chapter 2 presents a study in which a consonant vowel dichotic listening (DL) task, with forced attention conditions, was used to investigate the neuromodulatory effects of sex hormones on language lateralisation and cognitive control. Several previous studies (Cowell et al., 2011; Hampson, 1990a,1990b; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008) suggested that left hemispheric language dominance was increased during cycle phases associated with high levels of estradiol. However, this was not a consistent finding, with other studies suggested that high levels of estradiol led to a reduction in lateralisation (Alexander et al., 2002; Altemus et al., 1989; Mead & Hampson, 1996; Sanders & Wenmoth, 1998). Still further research showed that estradiol influenced lateralisation, but only when a high level of cognitive control was required (Hjelmervik et al., 2012). The study presented in Chapter 2 aimed to disentangle the effects of estradiol on top-down/bottom-up aspects of lateralisation. It was predicted that if gonadal steroid hormones primarily affected the bottom-up process related to language lateralisation, estradiol and/or progesterone would reduce the DL bias across all attention conditions. However, if high levels of gonadal hormones selectively affect top-down cognitive control, estradiol-related changes are expected only in the forced-left DL condition (Hjelmervik et al., 2012)

This study showed that language lateralisation was reduced when estradiol and

progesterone levels were high, across all attention conditions. This suggests that the effect of hormones on cognitive control is marginal, and that the neuromodulatory properties of sex hormones on lateralisation are due primarily to their influence over bottom-up processes. Given that the same effect was present for both right ear and left ear advantages, it is unlikely that the general reduction in language lateralisation is due to sex hormones selectively affecting one hemisphere. Instead, it was argued that this effect was due to the effect of sex hormones over interhemispheric inhibition. In line with this hypothesis, it was argued that the reduced REA in the non-forced and forced-right condition in participants with a relatively high level of estradiol might be due to reduced inhibition of the subdominant right hemisphere by the dominant left hemisphere. This would facilitate right hemisphere processing of stimuli presented to the left ear. Moreover, during the forced-left condition, it was argued that the top-down control process required to successfully divert attention away from the dominant right ear in favour of the left ear results in a shift of activation from the left hemisphere to the right hemisphere. As such, if estradiol is exacting a neuromodulatory effect on interhemispheric inhibition, the reduced LEA in the forced-left condition may be due to a reduction of inhibition from the right hemisphere over the left hemisphere. This would lead to an increase in left-hemispheric processingof stimuli presented to the right ear, and a reduction in the LEA.

Given that interhemispheric inhibition is a universal physiological process that underpins lateralisation, it follows that high estradiol levels should also reduce biases for tasks lateralised to the right hemisphere. The study presented in Chapter 3 was designed to investigate this notion, using two, differently lateralised dichotic listening tasks. In this study, a linguistic and an emotional prosody DL task were used, designed to assess left and right hemispheric lateralisation, respectively. For this study, it was hypothesised that if estradiol influenced the bottom-up processes of lateralisation (i.e. interhemispheric inhibition), reduced DL biases should be found in both tasks, regardless of the forced attention condition, when estradiol levels

are high. In contrast, if estradiol influenced cognitive control, increased DL biases should be found in the forced-left and forced-right conditions of the linguistic and emotional tasks, respectively.

In contrast to the previous chapter, and to the study hypotheses, no modulatory effect of sex hormones on language lateralisation was found. Moreover, in the emotional prosody task, high estradiol levels were only marginally associated with a reduction in lateralisation in the forced-right condition, suggesting that estradiol had a small effect on the top-down aspect of lateralisation in this task. However, this effect was driven by a small number of participants with particularly high estradiol levels. Critically, in this study, the degree of lateralisation yielded in both tasks was considerably larger than those in either Hodgetts et al. (2015a) or Hjelmervik et al. (2012). It was argued that was due to a strong, stimulus-driven (bottom-up) effect, which resulted in the task being less cognitively demanding. As such, it was suggested that the stimulus-driven effect was so strong that any sex hormonal effects on lateralisation were masked. It was also noted that the only DL condition to show any estradiol-related trends was the cognitive control (forced-right) condition of the emotional task. Moreover, this condition yielded the smallest DL bias, and the lowest target detection rate of all the forced-attention conditions. Thus, it was argued that these DL tasks associated with high target detection rates, and large laterality biases, are less susceptible to the modulatory effects of sex hormones which may be due to particularly strong stimulus-driven effects masking any sex hormone-related effect on cerebral lateralisation.

These studies, in conjunction with Hjelmervik et al. (2012) suggest that estradiol (and potentially progesterone) are, in principle, capable of modulating both top-down and bottom-up processes related to cerebral lateralisation. The study presented in Chapter 2 demonstrated that estradiol levels were related to a reduction in the stimulus-driven, bottom-up processes underpinning language lateralisation. Moreover, the study presented in Chapter 3 extends the

findings of Hjelmervik et al. (2012), by demonstrating that estradiol levels were related to a reduction in top-down processes in a right lateralised task. The low task demands, however, meant that this was a small effect. As such, the studies presented in Chapters 2 and 3 make an important contribution with respect to the inconsistencies reported in the literature concerning sex hormonal effects on lateralisation. Specifically, while these studies suggest that sex hormones do possess neuromodulatory properties that can influence functional cerebral lateralisation, these effects may be reduced when task demands are low.

Sex hormones, executive function, and schizotypy

Chapters 4 and 5 were designed to investigate the influence of estradiol on executive functioning in healthy participants with schizotypal personality traits. These studies were based on previous research, which suggested that estradiol can act as a neuroleptic agent against the psychotic symptoms of schizophrenia, such as delusions (Häfner, 2005; Kulkarni et al., 2013; Riecher-Rössler et al., 1994; Seeman & Lang, 1990), as well as modulate cognitive control processes in healthy participants (Hjelmervik et al., 2012; Jacobs & D'Esposito, 2011).

Chapter 4 presents a study in which participants completed the Deese-Roediger-McDermott paradigm, which is designed to elicit false memories. It was expected that participants with high levels of schizotypy would have more false memories than low schizotypy scorers and show overconfidence in these false memories, especially when their estradiol levels were low. Further, it was hypothesised that high levels of estradiol should have a beneficial effect, especially with respect to meta-cognitive control of false memories. This study showed that highly schizotypal participants with high estradiol produced significantly fewer false memories than those with low estradiol. There was no difference in the number of false memories between the high and low estradiol groups with low schizotypy. Moreover, highly schizotypal participants with high estradiol levels had less confidence in their false memories than those

with low estradiol, while low schizotypy participants with high estradiol were more confident in their false memories. Although these differences in confidence only approached significance, they suggest that estradiol may reduce false memory confidence, specifically in highly schizotypal participants. Interestingly, it may be argued that participants with low levels of schizotypy experienced a worsening of meta-memory with higher levels of estradiol, as evidenced by a higher KCI in this group. However, it could be argued that a lower KCI is not necessarily "beneficial". For example, it is possible that a lower KCI for error responses item type (i.e. new-related items) is reflective of a lower confidence in memories overall. This would result not only in a low level of confidence for false memories, but also lower confidence for correct responses (i.e. true memories). It is also noteworthy that while the low schizotypy participants yielded higher KCIs with higher estradiol, their number of false memories did not change, suggesting that a change in KCI does not affect the actual number of false memories produced.

Consequently, it was argued that the neuromodulatory effects of estradiol might be dependent upon individual differences in neurophysiology, and the properties associated those differences, that lead to individial differences in schizotypy. The mechanism underpinning this effect is unclear, but may be related to individual differences in dopaminergic activity between participants with high/low schizotypy. It has recently been suggested that the effect of estrogen on cognition is dependent on individual differences in baseline dopamine function (Colzato & Hommel, 2014; Barth et al., 2015).

The study presented in Chapter 5 aimed to extend the findings of Chapter 4 by including emotion as an influential factor over false memory rates and meta-memory. The results of this study showed an effect of emotionality on false memories. A higher number of false memories and greater overconfidence was found for the negative word lists, as compared to both the neutral and positive lists. Neutral words consistently produced the lowest number of false

memories and the lowest degree of false memory confidence. This effect occurred regardless of the participants' estradiol level, or degree of schizotypy, suggesting the effect of emotion of false memory formation and meta-memory is more robust than that of schizotypy or estradiol alone. This is supported by the concurrent lack of effect from estradiol or schizotypy on the number of false memories or false memory confidence for the critical lure items.

There was, however, an interaction between these three factors for the new-related items. This was due to an interaction between emotion and schizotypy in participants with a high level of estradiol. Although not statistically significant, highly schizotypal participants with high estradiol levels produced more false memories than less schizotypal participants for negative words, but fewer false memories for neutral and positive lists. This suggests that negative stimuli have a greater effect on false memory rates in highly schizotypal participants, particularly when estradiol is high.

There was also a significant interaction between emotion, estradiol and schizotypy with respect to false memory confidence. However, in contrast to the false memory rates, highly disorganised participants with a *low level of estradiol* were less confident in their false memories than participants with low schizotypy levels, for both the negative and the positive word lists. This contrasts the findings from the previous study (Hodgetts et al., 2015b), which showed that estradiol was beneficial to meta-memory in highly schizotypal participants. This selective enhancing effect of estradiol was explained in terms of individual differences in physiology between participants with different levels of cognitive disorganisation, such as a better ability to adapt to the increase in dopamine that is associated with higher estradiol levels, in highly schizotypal participants. In turn, a high level of estradiol resulted in improved (meta-) cognitive performance in these participants. In contrast, it might be that the combined effect of estradiol, emotion, and cognitive disorganisation on arousal resulted in dopaminergic function that was over the optimal level for good cognitive performance. Consequently, highly

schizotypal participants, with high estradiol levels performed particularly poorly in the emotional conditions. In contrast, those with a relatively low estradiol level have only the effect of emotion on their arousal levels, and thus, their performance is good. Critically, this does not explain why participants with low levels of schizotypy are considerably worse without estradiol.

Relationship between cognitive control and meta-memory

Given that the significant results presented in Chapters 2 and 4 were derived from the same sample of participants, it is possible to investigate potential relationships between the data sets presented in these chapters. Conducting such analyses may provide insight into the relationships that may exist between the different measures of executive function and cognitive control provided by the dichotic listening and meta-memory tasks. For example, subjecting the absolute LQs (presented in Chapter 2) to a mixed-model ANOVA with Condition as a within-subjects factor, and cognitive disorganisation (presented in Chapter 4), revealed an interaction between cognitive disorganisation and dichotic listening condition that appeared to approach significance[4]. Post-hoc tests revealed that highly schizoptypal participants produced significantly smaller asymmetries compared to those with lower schizotypy. This might suggest that high levels of cognitive disorganisation are characterised by a reduction in language lateralisation. This is in line with the clinical literature, suggesting that schizophrenia is characterised by atypical patterns of cerebral asymmetry (Løberg et al., 1999; Løberg et al., 2004; Oertel et al., 2010; Oertel-Knochel & Linden, 2011), and thus, supports use of schizotypy as a suitable non-clinical model of schizophrenia.

To further investigate possible relationships between the data presented in Chapters 2 and 4, a series of correlations were run between absolute LQs from the forced-left DL condition (Chapter 2) and

[4] Full details of these analyses can be found in Appendix ii and iii.

the KCIs from the new-related items in the meta-memory task (Chapter 4). Investigating the sample as a whole revealed a negative relationship between the absolute LQ from the forced-left condition and the new-related KCIs that was marginally significant. This suggests that participants yielding a high KCI (i.e. overconfidence in false memories) also exhibit poor cognitive control in the forced-left DL condition (i.e. a smaller absolute LQ). This lends support to the notion that meta-memory, and particularly memory confidence, is underpinned by the same top-down cognitive control process that is required by the forced-left DL condition. . Interestingly, this correlation becomes significant when only the High Estradiol group is considered while no such relationship is present in the Low Estradiol group. This might suggest that when estradiol levels are high, a similar physiological and/or cognitive mechanism is underpinning successful performance of both the meta-memory task, and the forced-left condition of the linguistic dichotic listening task. In contrast, when estradiol is low, the mechanisms underpinning these tasks differ, and as such, there is no relationship between the two variables. This explanation is clearly speculative, and further investigation, using multiple measures of executive function would be required in order to fully determine how sex hormones affect the relationships between different measures of similar cognitive processes.

Sex hormones and resting state connectivity

Chapter 6 presents a neuroimaging study designed to investigate sex and sex hormonal effects on two resting state networks. Specifically, this study aimed to investigate whether the neuromodulatory properties of estradiol and progesterone are specific to task-related activity, or if such effects were also present in resting-state activity. The functional connectivity of the auditory and default mode networks was investigated. A sample of young, naturally cycling women underwent three rs-fMRI scans, coinciding with the menstrual, follicular and luteal cycle phases. A sample of men was also scanned three times at corresponding time intervals. In line with previous resting state (Petersen et al., 2014) and behavioural studies in the same

cohort (Thimm et al., 2014), it was predicted that DMN connectivity would differ between the menstrual phase, and the follicular/luteal phases in women. The same network was predicted to be stable in men. In contrast, we predicted that connectivity within the auditory network would be stable, in both men and women, as it was previously suggested that hormonal effects in this network were related to stimulus-driven factors.

In the DMN, increased connectivity between regions of left PFC and the DMN was found in women during the menstrual phase, compared to the follicular and luteal phases. In contrast, DMN connectivity was stable in men. In the auditory network, no effect of cycle phase/session was found, and no interaction between cycle phase/session and sex was found. There was, however, a significant sex difference driven by a larger degree of connectivity in the superior temporal gyrus and the postcentral gyrus in men, as compared to women.

The finding of a menstrual cycle effect on DMN connectivity presents a number of implications, for both task-based and rs-fMRI. Specifically, this study suggests that DMN connectivity is not stable in women, and is confounded by hormonal fluctuations across the menstrual cycle. However, this cannot be generalised to other cognitive networks. This finding also has implications for behavioural studies. Critically, this finding suggests that the effect of gonadal steroid hormones on behaviours underpinned by regions of DMN (such as the medial PFC, orbitofrontal cortex and cingulate cortex) might depend on resting-state connectivity, as opposed to task-related activity.

The finding of a sex difference in connectivity, in conjunction with a lack of a cycle effect in the auditory network has a number of implications. Firstly, this suggests that sex differences in resting-state connectivity (at least for the auditory network) are present, regardless of the cycle phase in which women were tested. This suggests that resting-state connectivity might be a reflection of structural differences in connectivity between males and

females. A number of studies have demonstrated sex differences with respect to grey matter structure of auditory regions (e.g. superior temporal gyrus, Good et al., 2001; Schlaepfer et al., 1995). More recently, sex differences in white matter microstructure have been demonstrated in this region (Hsu et al., 2008). More importantly, this finding suggests that previously observed sex hormone effects in auditory-based tasks, such as those presented in Chapters 2 and 3, are likely due to sex hormone effects on task-related activity, and not on underlying resting states.

The findings presented in Chapter 6 also suggest that cognitive resting state networks are more sensitive to hormonal fluctuations than sensory networks are. Given that the DMN is primarily comprised of prefrontal cortical regions, it may be that this network is particularly sensitive to cycle effects due to the sensitivity of these regions to hormonal actions. In contrast, sensory networks appear to be less sensitive to sex hormones. This might suggest that hormonal effects on cognitive performance and/or functional brain organisation, at least for auditory-based tasks such as dichotic listening, are due to sex hormone effects on task-related brain activity and not due to changes in underlying sensory activity. Critically, the finding of a cycle effect in a frontal resting state network is in contrast to findings of Hjelmervik et al. (2014), who reported that sex hormonal fluctuations did not affect four, fronto-parietal "cognitive control" resting-state networks. However, as the study in the present thesis investigated only one cognitive and one sensory network, it is not possible to generalise this effect to other frontal resting state networks, such as those investigated by Hjelmervik et al. (2014). Indeed, given that Hjelmervik et al. (2014) investigated networks other than the DMN, it is possible that the hormone effect observed in the present thesis is specific to particular networks, underpinned by specific cortical regions (i.e. medial PFC regions).

Methodological issues

The main methodological issue for the present thesis stems from the use of young, naturally cycling women in each sample, as this may partly explain why the findings differ between Chapters 2 and 3, and 4 and 5. Previous physiological research suggests that a large proportion of younger women (aged 20-25 years) do not ovulate consistently during every cycle. For example, Metcalf and Mackenzie (1980) reported that only 62% of their sample of young women ovulated consistently for three consecutive cycles. Moreover, in a sub-sample of students, only 59.5% of young women ovulated consistently, while 83.5% of non-student women ovulated consistently. This is of particular relevance to the present thesis, as the majority of each sample was comprised of younger, female students. In addition, there is a great deal of inter-individual variation in cycle regularity and in cycle length. As such, there are likely to be differences between participants regarding when they ovulate and therefore, the cycle day on which the estradiol peak occurs (for a review see Hampson & Young, 2008). One option for future studies is to track several ovarian cycles for each participant, before participation. Indeed, reporting this data could prove useful to determining how much variation there is in these factors at population level. Alternatively, recruiting participants that have reached reproductive maturity (mid-20s as opposed to early 20s, Lipson & Ellison, 1992) may help reduce the amount of inter-individual variation in cycle length, anovulation, and cycle regularity. Indeed, Metcalfe and Mackenzie (1980) reported that 88% of women aged 25-29 ovulated consistently.

The potential lack of ovulation and inter-individual variation in cycle length may have underpinned the difference in specific hormone levels, and general hormone profiles between studies in the present thesis. For example, Chapters 4 and 5 both involved a sample of young women, classified as either High or Low estradiol, based on direct measures of salivary estradiol. However, there are considerable differences between the samples, particularly in their progesterone levels. In the first study, the High estradiol group yielded an average

progesterone level of 144 pg/ml, while in the second study the average progesterone level was 208 pg/ml. Perhaps even more critically, in the initial study the Low estradiol group yielded an average progesterone level of 77 pg/ml, while in the second study the comparable group yielded an average of 133 pg/ml. These differences in progesterone might be due to differences in ovulation rates between the samples. Moreover, given that progesterone has been shown to improve emotional memory formation (Ertman et al., 2011), this might explain why estradiol did not show an enhancing effect in Chapter 5.

The apparent difference in hormone levels/profiles between the samples in the present thesis highlights importance of directly measuring hormone levels, in addition to obtaining self-reports of cycle length, in menstrual cycle based studies. However, despite using such measures, the present thesis encountered problems such as participants exhibiting exceptionally high progesterone levels and sample contamination. This might suggest that an alternative, direct measure of hormone levels, such as blood samples, might yield more precise results. Indeed, blood plasma and serum assays offer the possibility of analysing other hormones that indicate ovulation (e.g. luteinising hormone and follicle stimulating hormone). Critically, these hormones do not pass into saliva. However, there are both practical and theoretical benefits to saliva sampling over blood sampling. Most obviously, saliva sampling is quick and non-invasive. This makes it possible for participants to collect their own sample, and allows for daily monitoring across cycles. Moreover, saliva, unlike blood, provides a measure of the biologically available estradiol (Quissell, 1993; see Lewis, 2006 for a review). This is the critical factor for behavioural studies aiming to examine the relationship between hormones, the brain, and behaviour. In contrast, current methods for measuring biologically available estradiol in blood are not precise (Vining & McGinley, 1986).

Implications

The findings of the present thesis add to the existing literature concerning the neuromodulatory effects of gonadal steroid hormones on the brain and behaviour in several ways. Firstly, the findings from Chapters 2 and 3 contribute to several ongoing debates concerning the mechanisms by which gonadal steroid hormones on affect brain lateralisation. Both of these studies suggest that the effect of estradiol on the top-down aspect of lateralisation (i.e., cognitive control) is smaller than previously suggested (Hjelmervik et al., 2012), as neither study reported an increase in lateralisation during the forced-attention conditions of the DL paradigms. However, while the findings of Chapter 2 suggested that estradiol was capable of influencing the bottom-up aspect of lateralisation (i.e. stimulus-driven interhemispheric inhibition), this was not replicated in Chapter 3. This was likely due to the greater degree of asymmetry produced by the tasks used in Chapter 3. This might suggest that estradiol effects on lateralisation are task-dependant, and that tasks which yield a large degree of asymmetry due to low task demands are unlikely to demonstrate hormonal effects. Taken together, these findings suggest that differences in the degree of asymmetry produced by an individual tasks might account for some of the inconsistencies in the literature regarding the effect of sex hormones on brain lateralisation. Given that large asymmetries are likely driven by bottom-up effects, this suggests that estradiol is only capable of influencing asymmetries when the bottom-up effects are not so strong as to mask any sex hormone effects lateralisation. This notion is strikingly similar to the aforementioned idea that the influence of estradiol on cognitive control is small and highly specific, and as such, was not replicated consistently throughout the studies presented here. As such, this suggests that the idea that sex hormones maintain general neuromodulatory properties that influence lateralisation is too simplistic. Instead, it is important to consider whether or not the lateralisation of a given cognitive process is driven by top-down or bottom-up processes, if we are to demonstrate a sex hormonal effect.

The results across all of the behavioural studies, both dichotic listening and meta-

memory, in the present thesis have important implications for our understanding of estradiol-related effects on executive function and cognitive control. Perhaps most importantly, they suggest that the notion of estradiol enhancing cognitive control (Colzato et al., 2012; Hampson, 1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002) is too simplistic. For example, the findings presented in Chapter 4 suggest that while estradiol might have an enhancing influence on meta-memory abilities, this effect is limited to those with a high level of particular schizotypal personality traits. Given that estradiol is known to influence activity in the dopaminergic system (for a recent review, see Barth et al., 2015), it is possible that the mechanism of this effect might be related to individual differences in neurophysiology that underpin individual differences in personality traits. Indeed, previous studies have suggested that high levels of schizotypy is associated with hyperdopaminergic function (Mohr et al., 2004; McClure et al., 2010). Thus, the increase in dopamine associated with high estradiol levels is unlikely to have produced the same effect in both high and low schizotypy. Instead, highly schizotypal participants may have been better able to adapt to higher dopamine levels.

Perhaps more importantly, the present thesis also directly contributes to the ongoing debate concerning the mechanisms by which gonadal steroid hormones exert their modulatory effects on brain organisation and cognition. Specifically, the reduced lateralisation presented in Chapter 2 suggests that a high level of estradiol reduced interhemispheric inhibition, and in turn, lateralisation (Hausmann & Güntürkün, 2000; Hausmann & Bayer, 2010). However, while the reduced lateralisation presented in Chapter 2 was driven primarily by estradiol, it is important to note that the High estradiol group also had higher progesterone levels. Thus, it is possible that high levels of estradiol might have reduced the interhemispheric inhibition, in combination with progesterone, as was previously suggested (see Hausmann & Bayer, 2010; Weis et al., 2011 for reviews), thereby decreasing lateralisation. Similarly, the failure to

replicate a selectively enhancing effect of estradiol between Chapters 4 and 5 might be due to the considerably higher level of progesterone in the latter sample. This is in line with an earlier notion purported by Smith (1994), who suggested that the excitatory effect of estradiol is dependent on its interaction with progesterone, and the presence of other steroids in the "background milieu" (p. 67). As such, the present thesis suggests that estradiol and progesterone can interact, but the consequences of this at the functional and behavioural level remains an important question for future research. In general, the findings from the present thesis suggest that is may be too simplistic to argue that estradiol is excitatory (via glutamatergic actions) and progesterone is inhibitory (via GABAergic actions).

Taken together, the findings presented in this thesis suggest that the effects of gonadal steroid hormones on the brain and cognition might be smaller, and more specific, than previously thought. In particular, whether or not sex hormone effects can be found, either on functional brain organisation and/or cognitive performance, appears to be contingent on the presence or absence of a number of additional factors. Such factors may be related to the specific task/cognitive process being assessed, individual differences in the neurophysiology of the participants under investigation, or an interaction between these factors. For example, with respect to lateralisation, the findings of the present thesis suggest that while estradiol (and progesterone) are capable of influencing the bottom-up, stimulus-driven process of lateralisation, and to some extent also top-down processes, this seems mainly mainly possible in tasks with relatively high cognitive demands. In contrast, tasks with low cognitive demands, which resulted in larger asymmetries in the current study, are less sensitive to the effects of sex hormones. Similarly, with respect to meta-memory, the present thesis suggests that the enhancing effect of estradiol is sensitive to individual differences, potentially due to underlying differences in neurophysiology. Moreover, this effect was found only for non-emotionally salient stimuli. Whether the effect of estradiol is similarly selective for other aspects of

executive function (e.g. response inhibition, set-switching) remains a question for future research, however, such a selective effect might help explain the presence of inconsistencies within the current literature.

Clinical implications

The findings of the present thesis also have some tentative clinical implications, particularly for the notion that estradiol acts as an antipsychotic in schizophrenia (Häfner, 2005; Riecher-Rössler et al., 1994; Kulkarni et al., 2013). For example, the findings in Chapter 4 suggest that estradiol could be beneficial for patients experiencing delusional symptoms, which are thought to be underpinned by a general susceptibility to forming false memories and maintaining them with a high degree of confidence. Moreover, given that schizophrenia has been associated with extensive deficits in executive function (Aas et al., 2014; Gold, 2004; Johnson-Selfridge & Zalewski, 2001; Roiser et al., 2013; Weisbrod et al., 2000), it is possible that estradiol could be beneficial to the cognitive symptoms of the illness. Critically, this finding was not replicated in Chapter 5. Instead, the findings presented here suggest that estradiol might be capable of influencing emotion processing in participants with a high level of schizotypy. However, given that difficulties in emotion processing have also been documented in schizophrenia (Kerns, 2006; Kucharska-Pietura & Klimkowski, 2002; Peters et al., 2013), it remains possible that estradiol could be beneficial for such patients. Alternatively, the lack of estradiol-related enhancement of meta-cognition in Chapter 5 might be due to the higher level of progesterone in this sample, relative to that presented in Chapter 4. Indeed, a recent study suggested that newly diagnosed patients with schizophrenia yielded higher levels of progesterone, compared to healthy controls (Bicikova et al., 2013). However, it is not yet clear whether progesterone alone might modulate schizophrenic symptomatology, or if this is due to an interactive effect with estradiol (Ko et al., 2006). It should also be noted that the results presented in Chapter 3 suggest that estradiol might actually be detrimental to cognitive

control. This is in line with the aforementioned notion that sex hormones can influence basic neurophysiology, with specific consequences for behaviour.

Findings from the present thesis also have some tentative implications for the notion of stratified medicine, which features highly in current NHS strategy. This notion has evolved from earlier conceptualisations of personalised or tailored treatment programmes, such as sex sensitive psychiatry. Sex sensitive psychiatry refers to the practice of medical care in such a way that the planning, delivery, and method of treatment is tailored to take sex differences into account. For example, with reference to schizophrenia, this might involve the tailoring of medication regimens to account for changes in symptom severity across the menstrual cycle. Indeed, findings from the present thesis suggest that there may be subsets of patients who may benefit from the addition of hormonal therapies, potentially as adjunctive therapies to a standard antipsychotic regimen. This is line with a number of early clinical studies that have demonstrated greater improvement in psychotic symptoms in patients given an adjunctive estradiol treatment (e.g. Kulkarni et al., 1996; 2001). Critically, while the present thesis investigated non-clincal models of schizophrenia, the findings suggest that adjunctive hormonal therapies may not be suitable for all patients. As such, the additional of such therapies may require a "trial and error" approach to treatment planning. This would involve altering medication regimens until the best combination is found for that particular patient. Such an approach has the obvious benefit of leading to a successful outcome for that particular patient. However, this approach could prove costly, both economically (time spent by clinicians working with individual cases, cost of multiple medications being administered in the short term) and personally for the patient. Critically, hormone therapies are characterised by a range of side effects, and it is currently not clear how they might interact with standard antipsychotic treatments. As such, while the present thesis suggests a need for stratified medicine to consider the use of hormonal therapies in the treatment of schizophrenia and psychosis, there is also a

clear need for further clinical research in order to fully determine how such treatments might be implemented.

Schizophrenia has also been consistently associated with atypical cerebral asymmetries (Løberg et al., 1999; Løberg et al., 2004; Oertel et al., 2010; Oertel-Knochel & Linden, 2011). Given that sex hormones are capable of influencing a number of processes related to lateralisation, a possible question for future research concerns the relationship between the modulation of asymmetries by gonadal hormones in atypically lateralised patients. Schizophrenia is also characterised aberrant functional connectivity in the DMN (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Garrity et al., 2007; Whitfield-Gabrieli et al., 2008). As such, the findings of a menstrual cycle effect on the DMN in the present thesis raises questions regarding how this network is affected by hormones in patients, and the potential behavioural consequences of this.

General conclusions

In conclusion, the present thesis contributes three novel findings to the literature regarding the neuromodulatory properties of sex hormones, and their influence on functional brain organisation and cognition. Firstly, it is suggested that sex hormones are capable of exerting neuromodulatory effects on the universal physiological processes underlying lateralisation, such as interhemispheric inhibition (Hausmann & Güntürkün, 1999; Hausmann & Güntürkün, 2000; Weis et al., 2008). However, they also suggest that the effect of hormones on brain asymmetry is dependent on task-related factors that underpin the strength of asymmetry. If there are strong bottom-up effects, making the task easy and with large asymmetries, the effect of sex hormones on lateralisation may be masked. Secondly, the findings from schizotypal participants suggest that the notion that cognitive control and executive function can be enhanced by estradiol (Colzato, Pratt, & Hommel, 2012; Hampson,

1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002) is too simplistic. Instead, it is suggested that estradiol effects on cognition are dependent upon individual differences in the neurophysiology underpinning specific cognitive abilities (e.g. the dopaminergic system). Finally, the rs-fMRI findings demonstrate that functional connectivity in the DMN are modulated by hormonal fluctuations during the menstrual cycle, while the functional connectivity in the auditory network is not affected. While this suggests that cognitive resting-state networks may be more susceptible to the effects of sex hormone fluctuations than sensory networks, this remains an open question. Taken together, the findings presented here highlight the effect of sex hormones on the brain, and on behaviours beyond those related to sexual reproduction. Furthermore, they suggest that sex hormone effects are more complex than previously hypothesised, underpinned by their capacity to interact with task demands, other hormones, and individual differences in neurophysiology.

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APPENDIX

Appendix i: Raw right and left ear reports.

Appendix ii: Details of analyses linking Chapters 2 and 4.

a) Cognitive Disorganisation effects in dichotic listening.
b) Correlations between knowledge corruption indices and absolute forced-left LQs.

Appendix i: Raw right ear and left ear reports

Table 1 Descriptive statistics for the number of right ear (RE) and left ear (LE) reports from Chapter 2 (mean ± standard deviation, range).

	Non-Forced RE	Non-Forced LE	Forced-Right RE	Forced-Right LE	Forced-Left RE	Forced-Left LE
Mean ± S.D.	15.43 ± 2.98	11.38 ± 2.46	19.36 ± 3.85	7.39 ± 2.99	8.89 ± 3.89	16.33 ± 3.96
Range	4 – 22	5 – 17	10 – 28	1 – 13	3 – 20	9 – 26

Table 2 Descriptive statistics for the number of right ear (RE) and left ear (LE) reports from the emotional prosody dichotic listening task Chapter 3 (mean ± standard deviation, range).

	Non-Forced RE	Non-Forced LE	Forced-Right RE	Forced-Right LE	Forced-Left RE	Forced-Left LE
Mean ± S.D.	20.67 ± 8.09	24.90 ± 7.66	24.29 ± 7.55	4.33 ± 6.60	3.75 ± 4.28	25.42 ± 7.64
Range	6 – 35	4 – 36	5 – 36	0 – 36	0 – 14	7 – 36

Table 3 Descriptive statistics for the number of right ear (RE) and left ear (LE) reports from the linguistic dichotic listening task Chapter 3 (mean ± standard deviation, range).

	Non-Forced RE	Non-Forced LE	Forced-Right RE	Forced-Right LE	Forced-Left RE	Forced-Left LE
Mean ± S.D.	26.56 ± 6.25	17.52 ± 7.90	30.85 ± 4.93	1.13 ± 1.39	4.08 ± 5.47	26.17 ± 7.01
Range	8 – 34	3 – 35	11 – 36	0 – 6	0 – 36	4 – 36

Appendix ii: Details of analyses linking Chapters 2 and 4

c) Cognitive Disorganisation effects in dichotic listening.

Absolute LQs (as given in Chapter 2) were subjected to a 3 × 2 mixed model ANOVA with Condition (non-forced, forced-right, forced-left) as within-subjects factors, and cognitive disorganisation (High CD, Low CD) as a between subjects factor. While the analysis revealed no significant overall difference between the CD groups with respect to the strength of asymmetry across conditions ($F_{(1,\ 71)}$ = 1.18, p = .281, η_p^2 = .016), the Condition × CD interaction approached significance ($F_{(1.55,\ 109.71)}$ = 2.69, p = .08, η_p^2 = .036). Post-hoc tests (Bonferroni) revealed that High CD participants produced significantly smaller asymmetries (M = 8.29, *S.D.* = 18.03) compared to the Low CD group (M = 20.63, *S.D.* = 19.64; $t_{(71)}$ = 2.79, p < .01). This might suggest that high levels of cognitive disorganisation are characterised by a reduction in language lateralisation. Interestingly, examination of the means suggested that participants with high levels of cognitive disorganisation produced larger asymmetries in the forced-left condition (M = 31.63, *S.D.* = 28.93) compared to less disorganised participants (M = 28.16, *S.D.* = 28.59). This might suggest better cognitive control abilities in cognitively disorganised participants. However, none of the post-hoc tests reached significance in the forced-attention conditions (both p > .05). Re-running the same analysis with the addition of Estradiol group (high, low) as a between subjects factor did not alter this finding. Moreover, the Condition × Estradiol × CD interaction was not significant ($F_{(1.55,\ 106.82)}$ = 0.79, p = 0.43, η_p^2 = .011).

d) Correlations between knowledge corruption indices and absolute forced-left LQs.

To further investigate possible relationships between the data presented in Chapters 2 and 4, a series of correlations were run between absolute LQs from the forced-left DL condition and the KCI from the new-related condition of the meta-memory task presented in Chapter 4.

Firstly, Pearson correlations using the sample as a whole (N = 73) revealed a negative relationship between KCI and the forced-left absolute LQ, that bordered significance (r = -.23, p = .053). This suggests that participants yielding a high KCI (i.e. overconfidence in false memories) also exhibit poor cognitive control in the forced-left DL condition (i.e. a smaller absolute LQ). This lends support to the notion that meta-memory, and particularly memory confidence, is underpinned by the same top-down cognitive control process that is required by the forced-left DL condition. Interestingly, this correlation is significant when only the High Estradiol group is considered (r = -.33, p = .049). The same relationship is not present in the Low Estradiol group (r = -.13, p = .46).

ADDENDUM

The articles presented in Chapters 2 and 4 have been published in international peer-reviewed journals. In addition, the article presented in Chapter 3 has been accepted for publication.

Published articles:

Hodgetts, S., Weis, S. & Hausmann, M. (2015). Sex hormones affect language lateralisation but not cognitive control in normally cycling women. *Hormones and Behavior* **74**: 194-200.

Hodgetts, S, Hausmann, M & Weis, S (2015). High estradiol levels improve false memory rates and meta-memory in highly schizotypal women. *Psychiatry Research,* **229**. 708 - 714

Accepted articles:

Hodgetts, S., Weis, S. & Hausmann, M. (2016). Estradiol-related variations in top-down and bottom-up processes of cerebral lateralisation. *Neuropsychology*.